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(71) Applicant (*for all designated States except US*): **COLEY PHARMACEUTICAL GROUP, INC.** [US/US]; 93 Worcester Street, Suite 101, Wellesley, MA 02481 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GRIESGRABER, George, W.** [US/US]; 631 Crimson Leaf Court, Eagan, MN 55123 (US). **JOHANNESSEN SLANIA, Sarah** [US/US]; 3712 Colfax Avenue South, Minneapolis, MN 55403 (US).

(74) Agent: **GATES, Edward, R.; Wolf, Greenfield & Sacks, P.C.**, 600 Atlantic Avenue, Boston, MA 02210 (US).

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(54) Title: SUBSTITUTED CHIRAL FUSED(1,2) IMIDAZO (4,5-C) RING COMPOUNDS AND METHODS

(57) Abstract: Substituted fused [1,2]imidazo[4,5-c] ring compounds (e.g., imidazo[4,5-c]quinolines, 6,7,8,9-tetrahydroimidazo[4,5-c]quinolines, imidazo[4,5-c]naphthyridines, 6,7,8,9-tetrahydroimidazo[4,5-c]naphthyridines, and imidazo[4,5-c]pyridines) with a -CHC-R2- group in the fused ring at the 2-position of the imidazo ring and a -CH(-R1)- group in the fused ring at the 1-position of the imidazo ring, pharmaceutical compositions containing the compounds, intermediates, methods of making the compounds, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases, are disclosed.

SUBSTITUTED CHIRAL FUSED [1,2]IMIDAZO[4,5-*c*] RING COMPOUNDS AND METHODS

5 This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Serial No. 60/807,155, entitled "SUBSTITUTED CHIRAL FUSED [1,2]IMIDAZO[4,5-*c*] RING COMPOUNDS AND METHODS" filed on July 12, 2006, which is herein incorporated by reference in its entirety.

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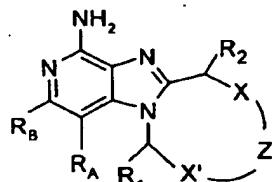
BACKGROUND

Certain compounds have been found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders. However, there continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other means.

15

SUMMARY

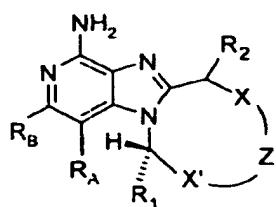
It has now been found that certain substituted chiral fused [1,2]imidazo[4,5-*c*] ring compounds are useful in modulating cytokine biosynthesis in animals. The present invention provides such compounds, which are of the following Formula I:



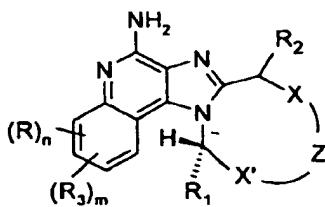
I

20

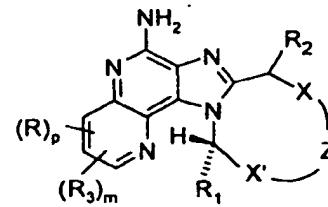
and, more particularly, compounds of the following Formulas II, III, IV, V, and VI:



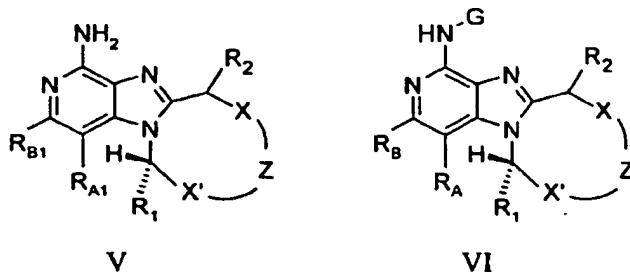
II



III



IV



wherein X, X', Z, R, R₁, R₂, R₃, R_A, R_B, R_{A1}, R_{B1}, G, m, n, and p are as defined below; and include pharmaceutically acceptable salts thereof.

5 The compounds and salts of Formulas I, II, III, IV, V, and VI are useful as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) or otherwise modulate the immune response when administered to animals. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the 10 compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of the compounds or salts of Formulas I, II, III, IV, V, and/or VI.

15 In another aspect, the present invention provides methods of inducing cytokine biosynthesis in animal cells, treating a viral disease in an animal, and/or treating a neoplastic disease in an animal by administering to the animal one or more compounds of the Formulas I, II, III, IV, V, and VI, and/or pharmaceutically acceptable salts thereof.

20 In another aspect, the invention provides methods of synthesizing the compounds of Formulas I, II, III, IV, V, and VI and intermediate compounds useful in the synthesis of these compounds.

As used herein, "a", "an", "the", "at least one", and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

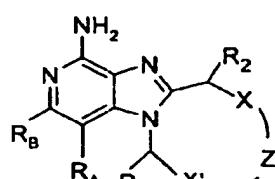
25 The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which

examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

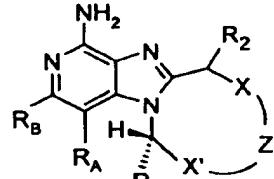
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

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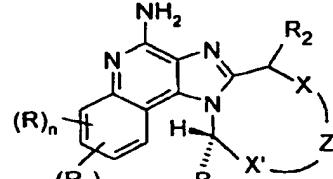
The present invention provides compounds of the following Formulas I, II, III, IV,
V, and VI:



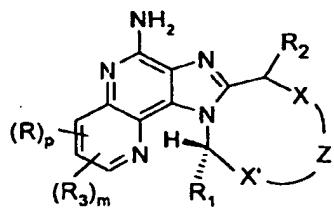
I



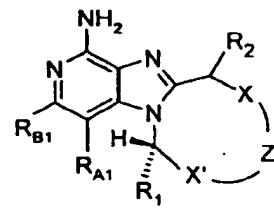
II



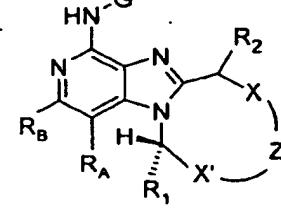
III



IV



V

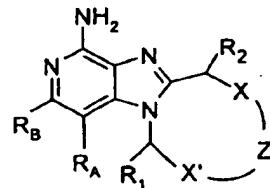


VI

10

wherein X, X', Z, R, R₁, R₂, R₃, R_A, R_B, R_{A1}, R_{B1}, G, m, n, and p are as defined below; and include pharmaceutically acceptable salts thereof.

In one embodiment, the present invention provides a compound of Formula I:



I

15

wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

20

X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

5 X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_{2a})-;

R₁ is selected from the group consisting of:

-X₁-R₄,

-X₁-Y'-R₄,

10 -X₁-Y'-X"-Y'-R₄, and

-X₁-R₅;

R₂ is selected from the group consisting of hydroxy, alkoxy, alkyl, and alkenyl wherein the alkyl group can be unsubstituted or substituted by one more substituents independently selected from the group consisting of alkoxy, amino, hydroxy, and 15 methanesulfonylamino;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

20 alkenyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

25 or when taken together, R_A and R_B form a fused aryl or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group;

30 or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

5 alkoxy,

alkylthio, and

-N(R₉)₂;

R₃ is selected from the group consisting of:

-Z'-R₄,

10 -Z'-X"-R₄,

-Z'-X"-Y'-R₄,

-Z'-X"-Y'-X"-Y'-R₄, and

-Z'-X"-R₅;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the
15 alkylene and alkenylene are optionally interrupted by one or more -O- groups, and
optionally substituted by a hydroxy or methoxy group;

X" is selected from the group consisting of alkylene, alkenylene, alkynylene,
arylene, heteroarylene, and heterocyclyene wherein the alkylene, alkenylene, and
20 alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or
heterocyclyene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

a bond,

-S(O)₂-,

-S(O)₂-N(R₈)-,

25 -C(R₆)-,

-C(R₆)-N(R₈)-,

-C(R₆)-N(R₈)-C(R₆)-,

-C(R₆)-N(R₈)-S(O)₂-, and

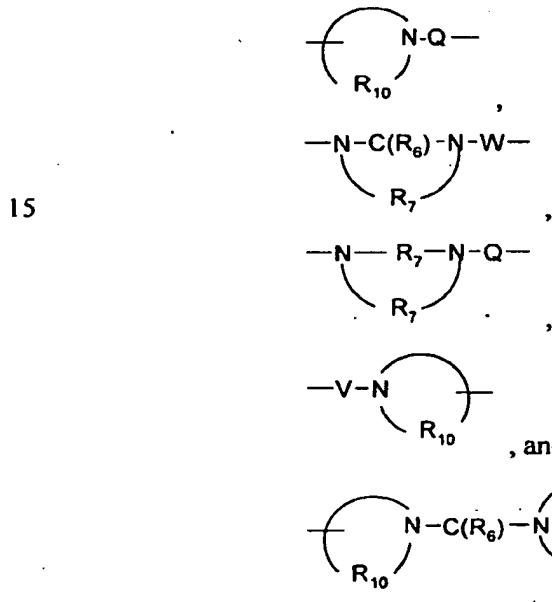
-C(R₆)-O-;

30 Y' is selected from the group consisting of:

-O-,

-S(O)₀₋₂-,

-S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-O-,
 -O-C(R₆)-,
 5 -O-C(O)-O-,
 -N(R₈)-Q-,
 -C(R₆)-N(R₈)-,
 -O-C(R₆)-N(R₈)-,
 -C(R₆)-N(OR₉)-,
 10 -O-N(R₈)-Q-,
 -O-N=C(R₄)-,
 -C(=N-O-R₈)-,
 -CH(-N(-O-R₈)-Q-R₄)-,



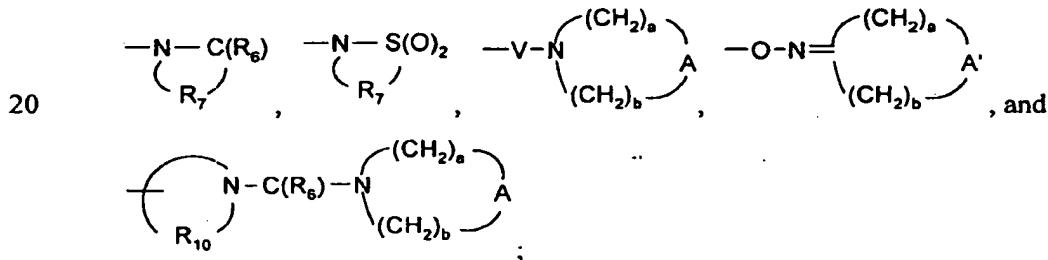
Z' is a bond or -O-;

20 R_{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups

can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxy carbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocycl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocycl, oxo; and, in the case of aryl, methylenedioxy;

5 R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylene, aryloxyalkylene, alkylarylene, heteroaryl, heteroarylalkylene, heteroaryloxyalkylene, alkylheteroarylene, and heterocycl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylene, aryloxyalkylene, alkylarylene, heteroaryl, heteroaryloxyalkylene, heteroaryl, heteroarylalkylene, heteroaryloxyalkylene, alkylheteroarylene, and heterocycl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; 10 nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocycl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocycl, oxo;

15 R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

25 R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylene, C_{1-10} alkoxy- C_{1-10} alkylene, aryl- C_{1-10} alkylene, and heteroaryl- C_{1-10} alkylene;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

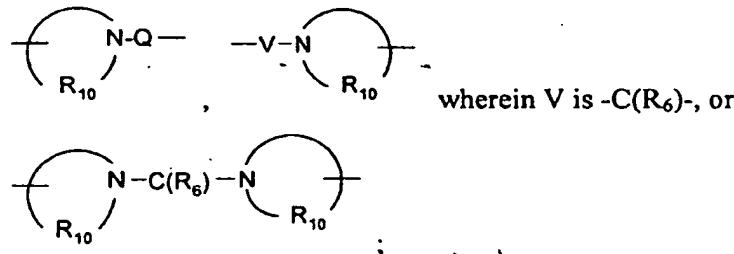
A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂₋, and -N(-Q-R₄)-;

A' is selected from the group consisting of -O-, -S(O)₀₋₂₋, -N(-Q-R₄)-, and -CH₂-;

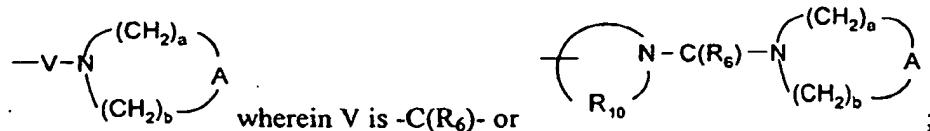
Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-,
 5 -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, -C(R₆)-S-, and -C(R₆)-N(OR₉)-;
 V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-,

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and
 a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;
 10 with the proviso that X₁ can also be a bond when:

Y' is bonded to X₁ and Y' is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-,
 -C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,

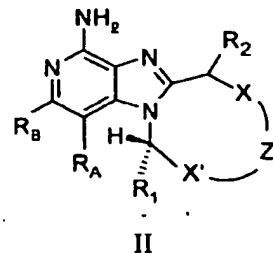


15 R₄ is bonded to X₁ and R₄ is other than hydrogen; or
 R₅ is bonded to X₁ and R₅ is



or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, the present invention provides a compound of
 20 Formula II:

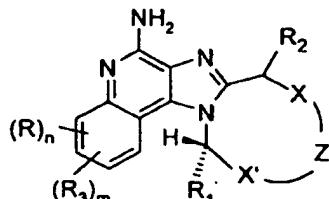


wherein:

X, X', Z, R₁, R₂, R_A, and R_B are defined as in Formula I above; or a pharmaceutically acceptable salt thereof.

In another preferred embodiment, the present invention provides a compound of Formula III:

5



III

wherein:

X, X', Z, R₁, R₂, R, and R₃ are defined as in Formula I above;

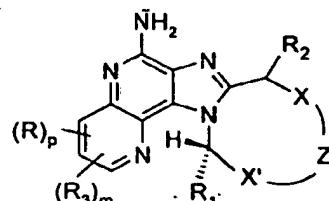
n is an integer from 0 to 4; and

10 m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In another preferred embodiment, the present invention provides a compound of Formula IV:

15



IV

wherein

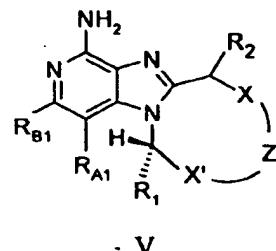
X, X', Z, R₁, R₂, R, and R₃ are defined as in Formula I above;

p is an integer from 0 to 3; and

m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

20 or a pharmaceutically acceptable salt thereof.

In another preferred embodiment, the present invention provides a compound of Formula V:



wherein:

X, X', Z, R₁, and R₂ are defined as in Formula I above;

5 R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

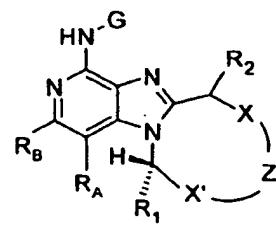
10 alkoxy,

alkylthio, and

-N(R₉)₂; and

R₉ is selected from the group consisting of hydrogen and alkyl; or a pharmaceutically acceptable salt thereof.

15 In another preferred embodiment, the present invention provides a compound of the Formula VI, which is a prodrug:



wherein:

20 G is selected from the group consisting of:

-C(O)-R',

α -aminoacyl,

α -aminoacyl- α -aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',
-C(=NY₂)-R',
-CH(OH)-C(O)-OY₂,
-CH(OC₁₋₄ alkyl)Y₀,
5 -CH₂Y₁, and
-CH(CH₃)Y₁;

R' and R" are independently selected from the group consisting of C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, 10 aryl-C₁₋₄ alkyl, heteroaryl-C₁₋₄ alkyl, halo-C₁₋₄ alkyl, halo-C₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃, -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂, with the proviso that R" can also be hydrogen;

15 α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y₂ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and benzyl;

Y₀ is selected from the group consisting of C₁₋₆ alkyl, carboxy-C₁₋₆ alkyl, amino-C₁₋₄ alkyl, mono-N-C₁₋₆ alkylamino-C₁₋₄ alkyl, and di-N,N-C₁₋₆ alkylamino-C₁₋₄ alkyl;

20 Y₁ is selected from the group consisting of mono-N-C₁₋₆ alkylamino, di-N,N-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C₁₋₄ alkylpiperazin-1-yl; and

X, X', Z, R₁, R₂, R_A, and R_B are defined as in Formula I above; or a pharmaceutically acceptable salt thereof.

25 The term "animal" as used herein includes animals such as, for example, humans, non-human primates, rodents, dogs, cats, horses, pigs, sheep, goats, cattle, and poultry.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., 30 cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a

total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylene", and "alkynylene" are used when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group 5 comprises an alkylene moiety to which an aryl group is attached.

Unless otherwise indicated, the term "halogen" refers to a halogen atom or one or more halogen atoms.

The term "haloalkyl" is inclusive of groups that are substituted by one or more 15 halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least 20 one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. In some embodiments, the term "heteroaryl" includes one ring that contains 2-5 carbon atoms, 1-3 heteroatoms, and O, S, and N as the heteroatoms. 25 Exemplary heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, 30 quinoxaliny, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocycl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially

unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. In some embodiments, the term "heterocyclyl" includes one ring that contains 2-5 carbon atoms, 1-3 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicyclic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclenyl" are used when "arylene", "heteroarylene", and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

The term "fused aryl ring" includes fused carbocyclic aromatic rings or ring systems. Examples of fused aryl rings include benzo, naphtho, fluoreno, and indeno.

The term "fused heteroaryl ring" includes the fused forms of 5 or 6 membered aromatic rings that contain one heteroatom selected from S and N. Examples of fused heteroaryl rings include pyrido and thieno.

The term "fused 5 to 7 membered saturated ring" includes rings which are fully saturated except for the bond where the ring is fused. In one example, the ring is a cyclohexene ring. In other examples wherein one heteroatom (N or S) is present, the ring is tetrahydropyrido or dihydrothieno.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula -N(R₉)₂ each R₉ group is independently selected. In another example, when a Y and a Y' group are both present and both contain an R₈ group, each R₈ group is independently selected. In a further example, when more than one Y' group is present (i.e., R₁ and R₃ each contains a Y' group) and each Y' group contains one or more R₇ groups, then each Y' group is independently selected, and each R₇ group is independently selected.

The invention is inclusive of the compounds described herein (including intermediates) in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, prodrugs, and the like. In particular, the invention specifically includes enantiomerically pure compounds, mixtures of enantiomers in any ratio, as well as racemic compounds. Ratios of a compound to its enantiomer include, for example, 50:50 or higher, 90:10 or higher, 95:5 or higher, 99:1 or higher, 99.9:0.1 or higher, or 100:0. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by various mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For any of the compounds presented herein, each one of the following variables (e.g., X, X', Y, Y', Z, R, R₁, R₂, R₃, R_A, R_B, R_{A1}, R_{B1}, G, m, n, and p and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would

be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments, R is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and -N(R₉)₂.

5 For certain embodiments, R is halogen or hydroxy.

For certain embodiments, R₁ is selected from the group consisting of -X₁-R₄, -X₁-Y'-R₄, -X₁-Y'-X"-Y'-R₄, and -X₁-R₅.

For certain embodiments, R₁ is -X₁-R₄.

For certain embodiments, R₁ is -X₁-Y'-R₄.

10 For certain embodiments, R₁ is -X₁-Y'-X"-Y'-R₄.

For certain embodiments, R₁ is -X₁-R₅.

For certain embodiments, R₁ is C₁₋₄ alkyl optionally substituted by hydroxy or one or more fluorine atoms.

15 For certain embodiments, R₁ is selected from the group consisting of methyl, isopropyl, 1-fluoro-1-methylethyl, 1-hydroxymethylethyl, phenyl, benzyl, and tetrahydro-2H-pyran-4-yl.

For certain embodiments R₁ is -X₁-Y'-R₄ wherein X₁ is C₂₋₅ alkylene, Y' is -NH-C(O)-, -S(O)₂-, or -NH-C(O)-NH-, and R₄ is C₁₋₃ alkyl.

20 For certain embodiments, R₂ is selected from the group consisting of hydroxy, alkoxy, alkyl, and alkenyl wherein the alkyl group can be unsubstituted or substituted by one more substituents independently selected from the group consisting of alkoxy, amino, hydroxy, and methanesulfonylamino.

25 For certain embodiments, R₂ is selected from the group consisting of hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkyl, and C₁₋₆ alkenyl wherein the alkyl group can be unsubstituted or substituted by one more substituents independently selected from the group consisting of C₁₋₃ alkoxy, amino, hydroxy, and methanesulfonylamino.

For certain embodiments, R₂ is selected from the group consisting of C₁₋₄ alkyl optionally substituted by C₁₋₃ alkoxy, amino, hydroxy, and methanesulfonylamino.

30 For certain embodiments, R₂ is selected from the group consisting of methyl, ethyl, n-propyl, aminomethyl, hydroxymethyl, methanesulfonylaminomethyl, and methoxymethyl.

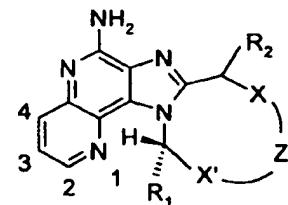
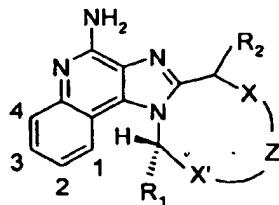
For certain embodiments, R_{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alcoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy.

For certain embodiments, R_{2a} is alkyl.

For certain embodiments, R_{2a} is methyl.

For certain embodiments, R₃ is selected from the group consisting of -Z'-R₄, -Z'-X"-R₄, -Z'-X"-Y'-R₄, -Z'-X"-Y'-X"-Y'-R₄, and -Z'-X"-R₅.

For certain embodiments, R₃ is at the 3-position with the positions numbered as follows:



For certain embodiments, R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino;

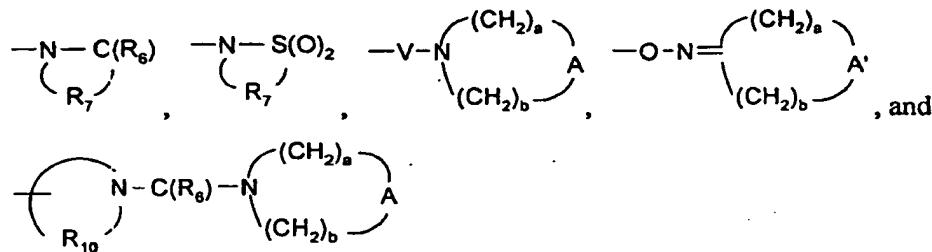
alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, o xo.

For certain embodiments, R₄ is alkyl or aryl.

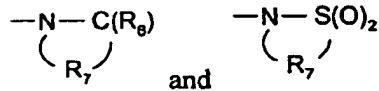
5 For certain embodiments, R₄ is alkyl optionally substituted by hydroxy or one or more fluorine atoms.

For certain embodiments, R₄ is phenyl.

For certain embodiments, R₅ is selected from the group consisting of:



10 For certain embodiments, R₅ is selected from the group consisting of:



For certain embodiments, R₆ is selected from the group consisting of =O and =S.

For certain embodiments, R₆ is =O.

For certain embodiments, R₇ is C₂₋₇ alkylene.

15 For certain embodiments, R₇ is C₂₋₅ alkylene.

For certain embodiments, R₇ is propylene.

For certain embodiments, R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, hydroxy-C₁₋₁₀ alkylene, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylene, aryl-C₁₋₁₀ alkylene, and heteroaryl-C₁₋₁₀ alkylene.

20 For certain embodiments, R₈ is hydrogen or C₁₋₄ alkyl.

For certain embodiments, R₈ is hydrogen or methyl.

For certain embodiments, R₈ is hydrogen.

For certain embodiments, R₉ is selected from the group consisting of hydrogen and alkyl.

25 For certain embodiments, R₉ is alkyl.

For certain embodiments, R₉ is hydrogen.

For certain embodiments, R₁₀ is C₃₋₈ alkylene.

For certain embodiments, R₁₀ is C₄₋₆ alkylene.

For certain embodiments, R₁₀ is pentylene.

For certain embodiments, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and -N(R₉)₂; or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group; or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

For certain embodiments, R_A and R_B form a benzo ring which is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group. For certain embodiments, R_A and R_B form a benzo ring which is unsubstituted.

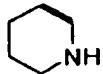
For certain embodiments, R_A and R_B form a pyrido ring which is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group. For certain embodiments, R_A and R_B form a pyrido ring which



is unsubstituted. For certain embodiments, the pyrido ring is wherein the highlighted bond indicates the position where the ring is fused.

For certain embodiments, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted. For certain embodiments, R_A and R_B form a fused cyclohexene ring that is unsubstituted or substituted by one, two, three, or four R groups. For certain embodiments, R_A and R_B form a fused cyclohexene ring that is unsubstituted.

For certain embodiments, R_A and R_B form a tetrahydropyrido ring that is unsubstituted or substituted on one or more ring carbon atoms by one, two, or three R groups. For certain embodiments, R_A and R_B form a tetrahydropyrido ring that is unsubstituted. For certain embodiments, the tetrahydropyrido ring is



wherein the highlighted bond indicates the position where the ring is fused.

For certain embodiments, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R_{A1} is hydrogen or alkyl and R_{B1} is alkyl.

5 For certain embodiments, R_{A1} and R_{B1} are each methyl.

For certain embodiments, A is selected from the group consisting of $-CH_2-$, $-O-$, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(-Q-R_4)-$.

For certain embodiments, A is $-O-$.

For certain embodiments, A is $-CH_2-$.

10 For certain embodiments, A is $-N(-Q-R_4)-$.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_{2-}$, $-C(R_6)-N(R_8)-W-$, $-S(O)_{2-}N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$.

For certain embodiments, Q is $-C(O)-$, $-S(O)_2$, $-S(O)_{2-}N(R_8)-$, or $-C(O)-N(R_8)-$.

15 For certain embodiments, Q is a bond.

For certain embodiments, V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_{2-}$.

For certain embodiments, W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_{2-}$.

20 For certain embodiments, W is a bond.

For certain embodiments, X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms.

For certain embodiments, X is a bond.

25 For certain embodiments, X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms.

For certain embodiments, X' contributes one ring carbon atom.

For certain embodiments, X' is C_{1-2} alkylene.

30 For certain embodiments, X' is methylene.

For certain embodiments, X' contributes two ring carbon atoms.

In each of the above embodiments of X and X', X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3.

For certain embodiments, X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group.

For certain embodiments, X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups.

For certain embodiments, X₁ is alkylene.

10 For certain embodiments, X₁ is C₁₋₄ alkylene.

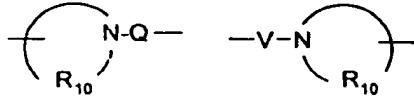
For certain embodiments, X₁ is methylene.

For certain embodiments, X₁ is C₁₋₃ alkylene optionally substituted by a hydroxy or methoxy group.

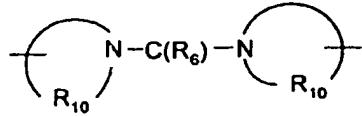
For certain embodiments, X₁ is -(CH₂)₁₋₃-.

15 For certain embodiments, X₁ is C₂₋₃ alkylene substituted by one hydroxy group.

For certain embodiments, X₁ is a bond, and the Y' bonded to X₁ is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,

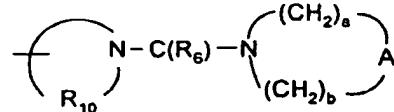


wherein V is -C(R₆)-, or



20 For certain embodiments, X₁ is a bond, R₄ is bonded to X₁, and R₄ is other than hydrogen.

For certain embodiments, X₁ is a bond, R₅ is bonded to X₁, and R₅ is



25 For certain embodiments, X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene,

alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclene and optionally interrupted by one or more -O- groups.

For certain embodiments, X' is alkylene.

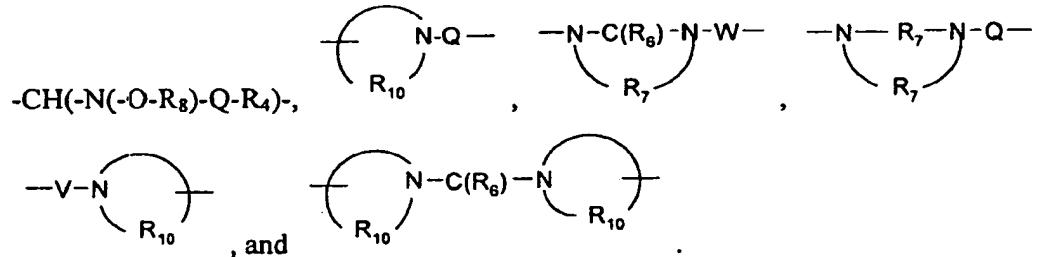
For certain embodiments, Y is selected from the group consisting of a bond,

5 -S(O)₂-, -S(O)₂-N(R₈)-, -C(R₆)-, -C(R₆)-N(R₈)-, -C(R₆)-N(R₈)-C(R₆)-,
-C(R₆)-N(R₈)-S(O)₂-, and -C(R₆)-O-.

For certain embodiments, Y is selected from the group consisting of -C(O)-, -S(O)₂-, and -C(O)NH-.

For certain embodiments, Y is -S(O)₂-.

10 For certain embodiments, Y' is selected from the group consisting of -O-, -S(O)₀₋₂-, -S(O)₂-N(R₈)-, -C(R₆)-, -C(R₆)-O-, -O-C(R₆)-, -O-C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, -O-C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-, -O-N(R₈)-Q-, -O-N=C(R₄)-, -C(=N-O-R₈)-,



15 For certain embodiments, Y' is -S-, -S(O)₂-, or N(R₈)-Q-.

For certain embodiments, Y' is -NH-S(O)₂-, -NH-C(O)-, -NH-S(O)₂-N(R₈)-, -NH-C(O)-N(R₈)-, -NH-C(S)-N(R₈)-, -NH-C(O)-O-, or -N(R₈)-.

For certain embodiments, Y' is -S- or -S(O)₂-.

For certain embodiments, Y' is -S(O)₂-.

20 For certain embodiments, Y' is -C(O)-.

For certain embodiments, Y' is -O-.

For certain embodiments, Z is selected from the group consisting of -O- and -N(Y-R_{2a})-.

For certain preferred embodiments, Z is -O-.

25 For certain embodiments, Z is -N(-Y-R_{2a})-.

For certain embodiments, Z' is a bond or -O-.

For certain embodiments, Z' is a bond.

For certain embodiments, Z' is -O-.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

For certain embodiments, a and b are each 2 or 3.

For certain embodiments, a and b are each 2.

5 For certain embodiments, m is 0 or 1.

For certain embodiments, m is 0.

For certain embodiments, m is 1.

For certain embodiments, n is an integer from 0 to 4.

For certain embodiments, n is 0.

10 For certain embodiments, n is 1.

For certain embodiments, n is 2.

For certain embodiments, n is 3 or 4.

For certain embodiments, p is an integer from 0 to 3.

For certain embodiments, p is 0.

15 For certain embodiments, p is 1.

For certain embodiments, m is 1 and n is 0.

For certain embodiments, m is 0 and n is 0.

For certain embodiments, m is 1 and p is 0.

For certain embodiments, m is 0 and p is 0.

20 In some embodiments, particularly embodiments of Formulas I, II, or VI, R_A and R_B form a benzo ring which is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group. For certain embodiments, R_A and R_B form a benzo ring which is unsubstituted.

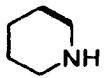
25 In some embodiments, particularly embodiments of Formulas I, II, or VI, R_A and R_B form a pyrido ring which is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group. For certain embodiments, R_A and R_B form a pyrido ring which is unsubstituted. For certain



embodiments, the pyrido ring is wherein the highlighted bond indicates the position where the ring is fused.

30 In some embodiments, particularly embodiments of Formulas I, II, or VI, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom

selected from the group consisting of N and S, wherein the ring is unsubstituted. For certain embodiments, R_A and R_B form a fused cyclohexene ring that is unsubstituted or substituted by one, two, three, or four R groups. For certain embodiments, R_A and R_B form a fused cyclohexene ring that is unsubstituted. For certain embodiments, R_A and R_B 5 form a tetrahydropyrido ring that is unsubstituted or substituted on one or more ring carbon atoms by one, two, or three R groups. For certain embodiments, R_A and R_B form a tetrahydropyrido ring that is unsubstituted. For certain embodiments, the tetrahydropyrido ring is



wherein the highlighted bond indicates the position where the ring is fused.

10 In some embodiments, particularly embodiments of Formulas I, II, or VI, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and -N(R₉)₂. For certain embodiments, R_A and R_B are each methyl.

15 In some embodiments, particularly embodiments of Formula V, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and -N(R₉)₂. In certain of these embodiments, R_{A1} and R_{B1} are each methyl.

In some embodiments, particularly embodiments of Formula III, n is an integer from 0 to 4. In certain of these embodiments, n is 0.

20 In some embodiments, particularly embodiments of Formula IV, p is an integer from 0 to 3. In certain of these embodiments, p is 0.

In some embodiments, particularly embodiments of Formula III, n is an integer from 0 to 4 and m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1. In certain of these embodiments, n and m are 0.

25 In some embodiments, particularly embodiments of Formula IV, p is an integer from 0 to 3, and m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1. In certain of these embodiments, p and m are 0.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, or VI, R is halogen or hydroxy.

30 In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments, Z is -N(-Y-R_{2a})-.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments (except where Z is -N(-Y-R_{2a})-), Z is -O-.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments (except where Z is -O-), Y is selected from the

5 group consisting of -C(O)-, -S(O)₂-, and -C(O)-NH-. In certain of these embodiments, Y is -S(O)₂-. For certain of these embodiments, R_{2a} is alkyl. For certain of these embodiments, R_{2a} is methyl.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments, R₁ is -X₁-R₄.

10 In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments (except when R₁ is -X₁-R₄), R₁ is -X₁-Y'-R₄.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments (except where R₁ is -X₁-R₄ or -X₁-Y'-R₄), R₁ is -X₁-Y'-X"-Y'-R₄.

15 In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments (except where R₁ is -X₁-R₄ or -X₁-Y'-R₄ or -X₁-Y'-X"-Y'-R₄), R₁ is -X₁-R₅.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments, X₁ is C₁₋₄ alkylene.

20 In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments where R₁ is -X₁-R₄, R₁ is C₁₋₄ alkyl optionally substituted by hydroxy or one or more fluorine atoms.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments wherein Y' is present, Y' is -C(O)-, -S(O)₂-, -N(R₈)-Q-, or -C(O)-NH-. In certain of these embodiments, Q is -C(O)-, -S(O)₂-, -S(O)₂-N(R₈)-, or -C(O)-N(R₈)-.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments wherein R₄ is present, R₄ is alkyl or aryl.

30 In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments where R₁ is -X₁-Y'-R₄ (except where X₁ is C₁₋₄ alkylene), X₁ is C₂₋₅ alkylene, and Y' is -NH-C(O)-, -S(O)₂-, or -NH-C(O)-NH-. For certain of these embodiments, R₄ is C₁₋₃ alkyl.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments (except where R₁ as defined does not include the following definition), R₁ is tetrahydro-2H-pyran-4-ylmethyl.

5 In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments, X is a bond.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments, X' contributes one ring carbon atom.

10 In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments, X' is C₁₋₂ alkylene. In certain of these embodiments, X' is methylene.

In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments (except where X' contributes one ring carbon atom or X' is methylene), X' contributes two ring carbon atoms.

15 In some embodiments, particularly embodiments of Formulas I, II, III, IV, V, VI, or any one of the above embodiments, R₂ is C₁₋₄ alkyl optionally substituted by C₁₋₃ alkoxy, amino, hydroxy, and methanesulfonylamino. For certain of these embodiments, R₂ is selected from the group consisting of methyl, ethyl, n-propyl, aminomethyl, hydroxymethyl, methanesulfonylaminomethyl, and methoxymethyl.

20 For certain embodiments of the compounds of Formulas I, II, III, IV, V, or any one of the above embodiments of these Formulas, the -NH₂ group can be replaced by an -NH-G group, as shown in the compounds of Formula VI, to form prodrugs. In such embodiments, G is selected from the group consisting of: -C(O)-R', α -aminoacyl, α -aminoacyl- α -aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY₂)-R', -CH(OH)-C(O)-OY₂, -CH(OC₁₋₄ alkyl)Y₀, -CH₂Y₁, and -CH(CH₃)Y₁. For certain embodiments, G is selected from the group consisting of -C(O)-R', α -aminoacyl, α -aminoacyl- α -aminoacyl, and -C(O)-O-R'. Preferably, R' and R" are independently selected from the group consisting of C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, phenyl, benzyl, and 2-phenylethyl each of which may be unsubstituted or substituted by one or more substitutents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, arylC₁₋₄ alkyl, heteroarylC₁₋₄ alkyl, haloC₁₋₄ alkyl, haloC₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃, -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂, with the proviso that R" can also be hydrogen. Preferably, α -aminoacyl is an acyl group

derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids. Preferably, Y₂ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and benzyl. Preferably, Y₀ is selected from the group consisting of C₁₋₆ alkyl, carboxyC₁₋₆ alkylenyl, aminoC₁₋₄ alkylenyl, mono-N-C₁₋₆ alkylaminoC₁₋₄ alkylenyl, and di-N,N-C₁₋₆ alkylaminoC₁₋₄ alkylenyl. Preferably, Y₁ is selected from the group consisting of mono-N-C₁₋₆ alkylamino, di-N,N-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C₁₋₄ alkylpiperazin-1-yl.

In some embodiments, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of Formulas I, II, III, IV, V, VI, or any one of the above embodiments and a pharmaceutically acceptable carrier.

In some embodiments, the present invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of Formulas I, II, III, IV, V, VI, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas I, II, III, IV, V, VI or any one of the above embodiments of these Formulas to the animal. For certain of these embodiments, the cytokine is selected from the group consisting of IFN- α , TNF- α , IL-6, IL-10, and IL-12. For certain of these embodiments, the cytokine is IFN- α or TNF- α . For certain of these embodiments, the cytokine is IFN- α .

In some embodiments, the present invention provides a method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas I, II, III, IV, V, VI, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas I, II, III, IV, V, VI, or any one of the above embodiments of these Formulas to the animal.

In some embodiments, the present invention provides a method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas I, II, III, IV, V, VI, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas I, II, III, IV, V, VI, or any one of the above embodiments of these Formulas to the animal.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritzky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

In some of the Reaction Schemes below, the product may be obtained as a racemic or scalemic mixture; particularly, if a racemic starting material is used. A mixture thus prepared can be resolved by methods known to one skilled in the art, for example, by chiral chromatography or by reacting the mixture with an enantiomerically pure sulfonic acid or carboxylic acid and selectively crystallizing a salt of one of the enantiomers from the mixture.

In some embodiments, compounds of the invention can be prepared according to Reaction Scheme I, wherein R, R₄, X₁, and X' are as defined above; E is carbon (imidazoquinolines) or nitrogen (imidazonaphthyridines); n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring); and R_{2b} is alkyl or alkoxy.

In step (1) of Reaction Scheme I, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XX is treated with an amino alcohol of Formula XXI to provide a compound of Formula XXII. Several amino alcohols of Formula XXI are commercially available, such as (S)-1-amino-2-propanol, L-valinol, (S)-2-phenylglycinol, and (S)-2-amino-3-phenyl-1-propanol. Others can be prepared by known synthetic methods; for example, see the methods described in Williams, L. et al., *Tetrahedron*, 52, pp. 11673-11694, (1996) and Genevois-Borella, A. et al., *Tetrahedron Lett.*, 31, pp. 4879-4882 (1990) for the preparation of amino alcohols wherein R₄ includes a hydroxy substituent. A hydroxy substituent on R₄ can readily be converted to a halogen substituent using a variety of known methods; for example, a hydroxy substituent can be converted to a fluoro substituent using (diethylaminosulfur) trifluoride in a suitable solvent such as dichloromethane at a sub-ambient temperature such as -78 °C.

The reaction in step (1) can be carried out by adding the amino alcohol of Formula XXI to a solution of a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XX in a suitable solvent such as dichloromethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at

a sub-ambient temperature such as 0 °C. Many compounds of Formula XX are known or can be prepared using known synthetic methods; see, for example, U.S. Patent Nos. 4,689,338; 5,175,296; 5,367,076; 5,389,640; and 6,194,425; U.S. Patent Application Publication No. US 2004/0147543; and International Publication Nos. WO 2005/123080 and WO 2006/038923; and the documents cited therein.

5 In step (2) of Reaction Scheme I, a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula XXII is reduced to provide a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XXIII. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation can be carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, isopropanol, ethyl acetate, acetonitrile, or mixtures thereof. The reaction can be carried out at ambient temperature.

10 In step (3) of Reaction Scheme I, a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XXIII is reacted with a carboxylic acid equivalent, which is selected such that it will provide the desired -CH₂-R_{2b} substituent in a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIV. Suitable carboxylic acid equivalents include ortho esters, acid halides, imidates, and imidate salts.

15 When the carboxylic acid equivalent is an ortho ester of Formula R_{2b}-CH₂C(O-alkyl)₃ wherein R_{2b} is alkyl, the reaction can be carried out by combining a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XXIII with the ortho ester in a suitable solvent such toluene. Optionally, a catalytic amount of pyridine hydrochloride can be added. The reaction can be carried out at an elevated temperature such as 85 – 90 °C.

20 When the carboxylic acid equivalent is an acid halide of Formula R_{2b}-CH₂-C(O)Cl or R_{2b}-CH₂-C(O)Br, the reaction can be carried out by adding an excess of the acid halide to a solution of a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XXIII in a suitable solvent such as dichloromethane or 1,2-dichloroethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at a sub-ambient temperature.

25 The reaction with an acid halide can be carried out in three parts, which include (i) adding the acid halide to a solution of a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XXIII in a suitable solvent such as chloroform, dichloromethane, or

1,2-dichloroethane optionally in the presence of a tertiary amine such as triethylamine to afford an amide intermediate in which the alcohol group has been acylated, (ii) cyclizing to provide a $1H$ -imidazo[4,5-*c*]quinoline or $1H$ -imidazo[4,5-*c*][1,5]naphthyridine in which the alcohol group is acylated, and (iii) removing the acyl group to provide a $1H$ -imidazo[4,5-*c*]quinoline or $1H$ -imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIV. The amide intermediate from part (i) can be optionally isolated using conventional techniques. The cyclization in part (ii) can be carried out by heating the amide intermediate from part (i) in a suitable solvent such as toluene. The cyclization in part (ii) can also be carried out in the presence of a base such as triethylamine or in the presence of an acid such as glacial acetic acid. The acylated intermediate from part (ii) can be isolated using conventional techniques. The removal of the acyl group in part (iii) can be effected by treating a solution of the intermediate from part (ii) in a suitable solvent mixture such as ethanol and water with potassium carbonate at an elevated temperature such as 60 °C.

When the carboxylic acid equivalent is an imidate of Formula R_{2b}-CH₂-C(=NH)-O-alkyl or a salt thereof, the reaction can be carried out by combining a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XXIII with the imidate in a suitable solvent such 1,2-dichloroethane, chloroform, or propyl acetate. The reaction can be carried out at an elevated temperature such as 55 - 85 °C or at the reflux temperature of the solvent. If the imidate reacts with the alcohol group, the product can be treated with potassium carbonate as described above to provide a $1H$ -imidazo[4,5-*c*]quinoline or $1H$ -imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIV. Some imidates of Formula R_{2b}-CH₂-C(=NH)-O-alkyl are known; others can be prepared by known methods.

In step (4) of Reaction Scheme I, a $1H$ -imidazo[4,5-*c*]quinoline or $1H$ -imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIV is cyclized to provide a compound of Formula XXV. The reaction can be carried out by treating a suspension of a compound of Formula XXIV in a suitable solvent such as carbon tetrachloride with *N*-bromosuccinimide. The reaction can be carried out at an elevated temperature such as the reflux temperature of the solvent. Optionally, the reaction mixture can be exposed to ultraviolet light.

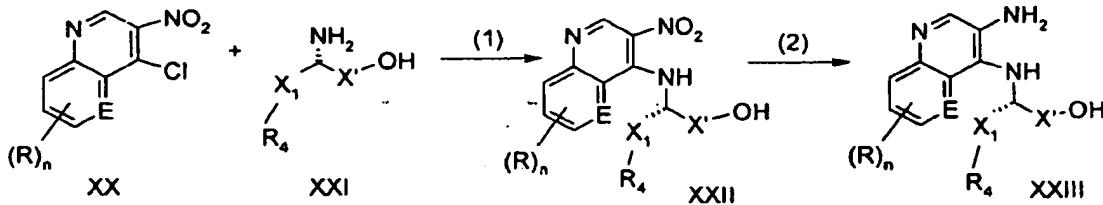
In step (5) of Reaction Scheme I, a $1H$ -imidazo[4,5-*c*]quinoline or $1H$ -imidazo[4,5-*c*][1,5]naphthyridine of Formula XXV is oxidized to provide a $1H$ -imidazo[4,5-*c*]quinoline-5*N*-oxide or $1H$ -imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of

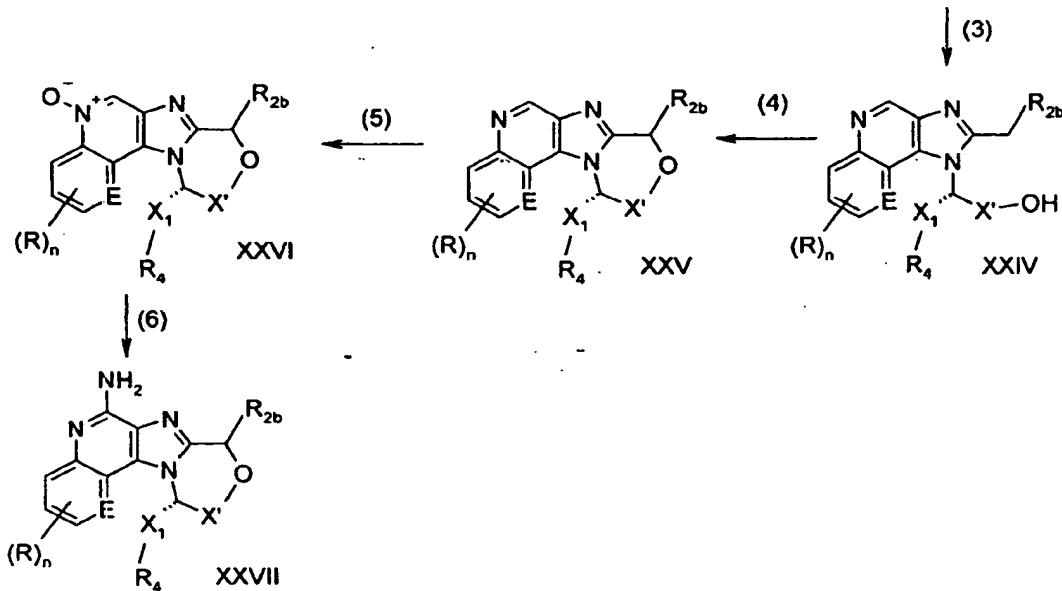
Formula XXVI using a conventional oxidizing agent capable of forming *N*-oxides. The reaction can be carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXV in a suitable solvent such as chloroform or dichloromethane. The reaction can be carried out at ambient temperature.

In step (6) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XXVI is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXVII, a subgenus of Formulas I, II, III, and IV. Step (6) involves the activation of an *N*-oxide of Formula XXVI by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction can be carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XXVI in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature.

Alternatively, the oxidation and amination can be carried out as a one-pot procedure without isolating the *N*-oxide of Formula XXVI by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXV in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride.

Reaction Scheme I





In some embodiments, compounds of the invention can be prepared according to Reaction Scheme II, wherein R, X₁, and X' are as defined above; E is carbon (imidazoquinolines) or nitrogen (imidazonaphthyridines); n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring); Boc is *tert*-butoxycarbonyl;

5 R_{1a} is -X₁-N(R₈)-Q-R₄ or -X₁-R_{5a}, wherein R_{5a} is $\begin{array}{c} \text{---N---C(R}_6\text{)} \\ | \\ \text{---R}_7\text{---} \end{array}$, $\begin{array}{c} \text{---N---S(O)}_2 \\ | \\ \text{---R}_7\text{---} \end{array}$, or

$$\begin{array}{c} (\text{CH}_2)_a \\ \text{---V---N---A---} \\ | \\ (\text{CH}_2)_b \end{array}$$
, wherein V is -N(R₈)-C(R₆)-; and R_{2b} is alkyl or alkoxy.

In step (1) of Reaction Scheme II, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XX is treated with compound of Formula XXVIII to provide a compound of Formula XXIX. Compounds of Formula XXVIII can be prepared by conventional synthetic methods from chiral, enantiomerically pure, commercially available starting materials such as L-ornithine hydrochloride and D-serine methyl ester hydrochloride. For example, the two amino groups of L-ornithine can be protected with two different protecting groups, such as a Boc group and a benzyloxycarbonyl group (Masiukiewicz, *Org. Prep. Proced. Int.* 34, 531-537, (2002)), and then the carboxylic acid group can be reduced to a hydroxy group. One of the amino groups can then be selectively deprotected for reaction in step (1). The methods described in Pickersgill, I. F.

and Rapoport, H., *J. Org. Chem.*, 65, pp. 4048-4057, (2000) can also be used to prepare compounds of Formula XXVIII.

The reaction in step (1) can be carried out by adding the protected amino alcohol of Formula XXVIII to a solution of a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XX in a suitable solvent such as dichloromethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at an elevated temperature such as, for example, the reflux temperature of the solvent.

In steps (2) through (6) of Reaction Scheme II, a of 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XXIX is converted to a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXX, a subgenus of Formulas I, II, III, and IV. The steps can be carried out using the methods described in steps (2) through (6) of Reaction Scheme I.

In step (7) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXX is treated with acid to effect removal of the Boc group to provide a compound of Formula XXXI, a subgenus of Formulas I, II, III, and IV. The reaction can be carried out by treating a compound of Formula XXX with hydrogen chloride in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature or at an elevated temperature, such as the reflux temperature of the solvent.

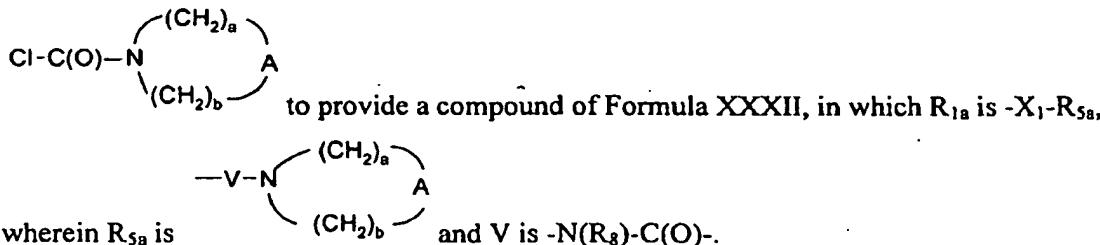
In step (8) of Reaction Scheme II, the amino group of a compound of Formula XXXI, revealed in step (7), or a salt thereof is converted to an amide, sulfonamide, sulfamide, or urea of Formula XXXII using conventional methods. For example, a compound of Formula XXXI or a salt thereof can react with an acid chloride of Formula R₄C(O)Cl to provide a compound of Formula XXXII in which R_{1a} is -X₁-N(R₈)-Q-R₄, and Q is -C(O)-. In addition, a compound of Formula XXXI can react with a sulfonyl chloride of Formula R₄S(O)₂Cl or a sulfonic anhydride of Formula (R₄S(O)₂)₂O to provide a compound of Formula XXXII in which R_{1a} is -X₁-N(R₈)-Q-R₄ and Q is -S(O)₂-.

Numerous acid chlorides of Formula R₄C(O)Cl, sulfonyl chlorides of Formula R₄S(O)₂Cl, and sulfonic anhydrides of Formula (R₄S(O)₂)₂O are commercially available; others can be readily prepared using known synthetic methods. The reaction can be carried out by adding the acid chloride of Formula R₄C(O)Cl, sulfonyl chloride of Formula R₄S(O)₂Cl,

or sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to a solution of the compound of Formula XXXI in a suitable solvent such as chloroform, dichloromethane, *N,N*-dimethylformamide (DMF), or *N,N*-dimethylacetamide (DMA). Optionally, a base such as triethylamine, *N,N*-diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or combinations thereof can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C.

5 Ureas of Formula XXXII, where R_{1a} is $-X_1-N(R_8)-Q-R_4$, Q is $-C(O)-N(R_8)-$, and R_8 is hydrogen, can be prepared by reacting a compound of Formula XXXI or a salt thereof with isocyanates of Formula $R_4N=C=O$. Numerous isocyanates of Formula $R_4N=C=O$ are 10 commercially available; others can be readily prepared using known synthetic methods. The reaction can be carried out by adding the isocyanate of Formula $R_4N=C=O$ to a solution of the compound of Formula XXXI in a suitable solvent such as DMF, chloroform, dichloromethane, or DMA. Optionally, a base such as triethylamine, *N,N*-diisopropylethylamine, DBU, or combinations thereof can be added. The reaction can be 15 carried out at ambient temperature or a sub-ambient temperature such as 0 °C.

15 Alternatively, a compound of Formula XXXI can be treated with an isocyanate of Formula $R_4(CO)N=C=O$, a thioisocyanate of Formula $R_4N=C=S$, a sulfonyl isocyanate of Formula $R_4S(O)_2N=C=O$, or a carbamoyl chloride of Formula $R_4N-(R_8)-C(O)Cl$ to provide a compound of Formula XXXII, where R_{1a} is $-X_1-N(R_8)-Q-R_4$ and Q is $-C(O)-N(R_8)-C(O)-$, 20 $-C(S)-N(R_8)-$, $-C(O)-N(R_8)-S(O)_2-$, or $-C(O)-N(R_8)-$, respectively. Alternatively, a compound of Formula XXXI can be treated with a carbamoyl chloride of Formula



25 Sulfamides of Formula XXXII, where R_{1a} is $-X_1-N(R_8)-Q-R_4$ and Q is $-S(O)_2-N(R_8)-$, can be prepared by reacting a compound or salt of Formula XXXI with sulfonyl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of formula $HN(R_8)R_4$. Alternatively, sulfamides of Formula XXXII can be prepared by reacting a compound of Formula XXXI with a sulfamoyl chloride of formula $R_4(R_8)N-S(O)_2Cl$. Many sulfonyl chlorides of Formula $R_4S(O)_2Cl$ and

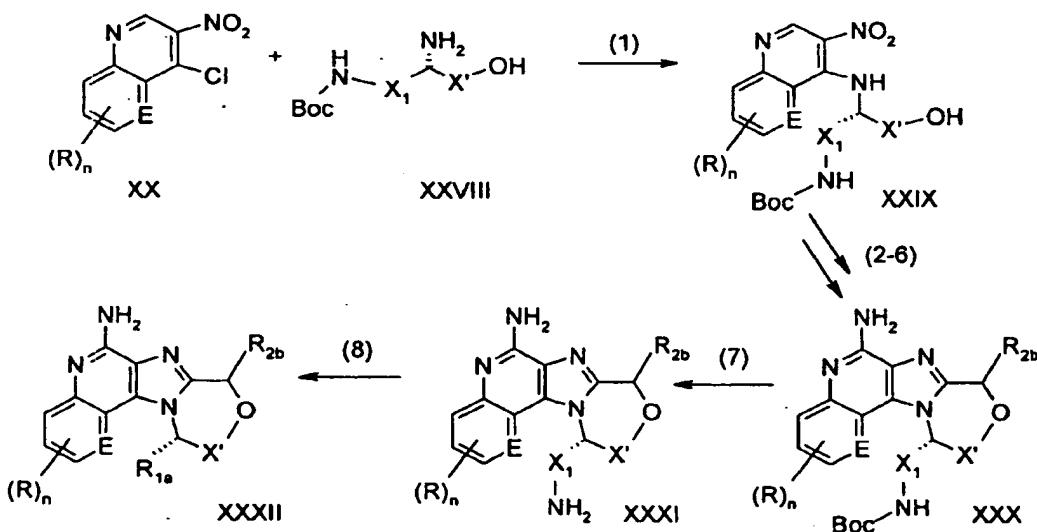
amines of Formula $\text{HN}(\text{R}_8)\text{R}_4$, and some sulfamoyl chlorides of formula $\text{R}_4(\text{R}_8)\text{N}-\text{S}(\text{O})_2\text{Cl}$ are commercially available; others can be prepared using known synthetic methods.

Additionally, a compound or salt of Formula XXXI can be reacted with a chloroalkanesulfonyl chloride of Formula $\text{Cl}-\text{R}_7-\text{S}(\text{O})_2\text{Cl}$ or a chloroalkanoyl chloride compound of formula $\text{Cl}-\text{R}_7-\text{C}(\text{O})\text{Cl}$ to provide a compound of Formula XXXII, wherein

—N—S(O)₂ —N—C(O)
 $\left(\begin{array}{c} | \\ \text{R}_7 \end{array} \right)$ or $\left(\begin{array}{c} | \\ \text{R}_7 \end{array} \right)$

R_{1a} is -X₁-R_{5a} and R_{5a} is a ring having the structure
 respectively. The reaction can be carried out by adding the chloroalkanesulfonyl chloride or chloroalkanoyl chloride to a solution of a compound of Formula XXXI in a suitable solvent such as dichloromethane in the presence of a base such as triethylamine or *N,N*-diisopropylethylamine. The intermediate chloroalkanesulfonamide or chloroalkanamide may optionally be isolated before treatment with a stronger base such as DBU at ambient temperature. If the intermediate chloroalkanesulfonamide or chloroalkanamide is isolated, the reaction with DBU can be carried out in a suitable solvent such as DMF.

Reaction Scheme II



15

In some embodiments, compounds of the invention can be prepared according to Reaction Scheme III, wherein R_{A1}, R_{B1}, R₄, X₁, and X' are as defined above; Bn is benzyl; and R_{2b} is alkyl or alkoxy.

In step (1) of Reaction Scheme III, a 2,4-dichloro-3-nitropyridine of Formula XXXIII is reacted with a compound of Formula XXI to form a 2-chloro-3-nitropyridine of

Formula XXXIV. Step (1) of Reaction Scheme III can be carried out according to the methods described in step (1) of Reaction Scheme I. Many 2,4-dichloro-3-nitropyridines of the Formula XXXIII are known and can be readily prepared using known synthetic methods; see, for example, U.S. Pat. No. 6,525,064 and the references cited therein.

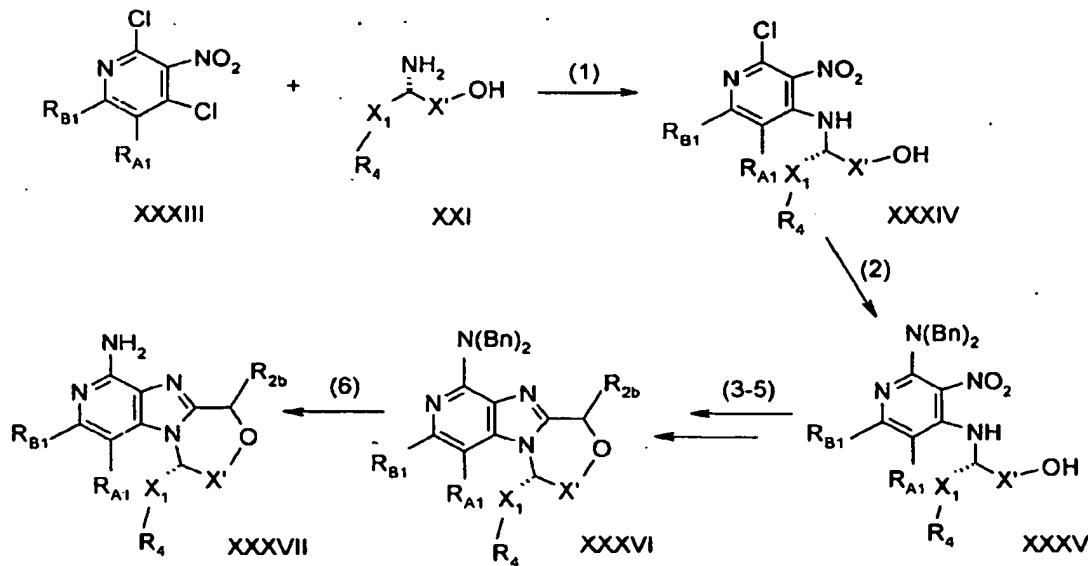
5 In step (2) of Reaction Scheme III, a 2-chloro-3-nitropyridine of Formula XXXIV is treated with dibenzylamine to provide an N^2 -dibenzyl-3-nitropyridin-2,4-diamine of Formula XXXV. The reaction can be carried out by combining the compound of Formula XXXIV with dibenzylamine and a tertiary amine such as triethylamine in a suitable solvent such as toluene. The reaction can be carried out at an elevated temperature.

10 In steps (3) through (5) of Reaction Scheme III, an N^2 -dibenzyl-3-nitropyridin-2,4-diamine of Formula XXXV is converted to a compound of Formula XXXVI using the methods described in steps (2) through (4) of Reaction Scheme I.

15 In step (6) of Reaction Scheme III, the benzyl groups of a compound of Formula XXXVI are cleaved using transfer hydrogenation to provide a $1H$ -imidazo[4,5-*c*]pyridin-6-amine of Formula XXXVII, a subgenus of Formulas I, II, and V. The reaction can be carried out by adding ammonium formate to a solution of a compound of Formula XXXVI in a suitable solvent such as ethanol or methanol in the presence of a catalyst such as palladium on carbon. The reaction can be carried out at an elevated temperature, for example, the reflux temperature of the solvent.

20

Reaction Scheme III



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme IV, wherein R_{A1}, R_{B1}, R_{1a}, X₁, X', and Boc are as defined above; and R_{2b} is alkyl or alkoxy.

5 In step (1) of Reaction Scheme IV, a 2,4-dichloro-3-nitropyridine of Formula XXXIII is reacted with a compound of Formula XXVIII to form a 2-chloro-3-nitropyridine of Formula XXXVIII. Step (1) of Reaction Scheme IV can be carried out according to the methods described in step (1) of Reaction Scheme II.

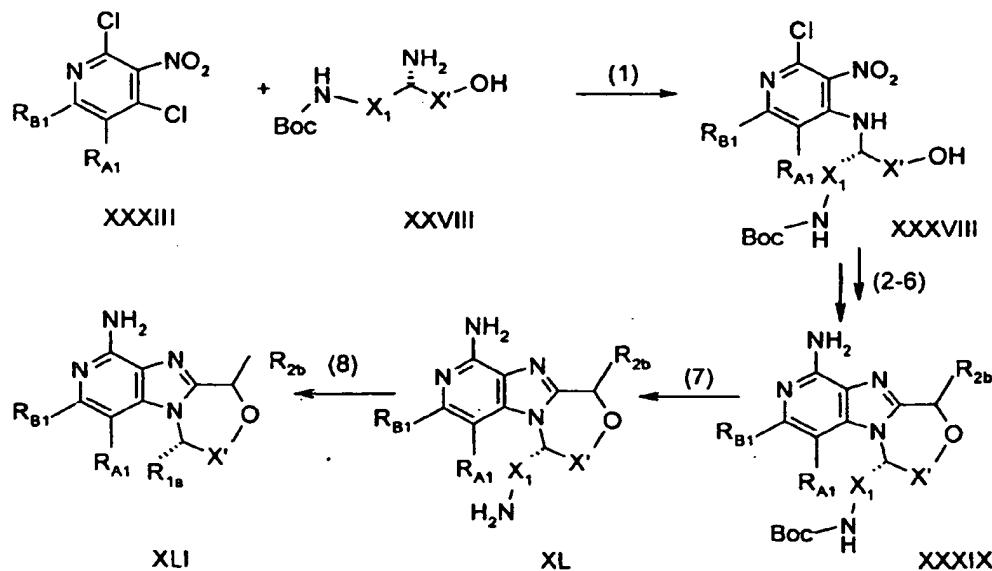
10 In steps (2) through (6) of Reaction Scheme IV, a 2-chloro-3-nitropyridine of Formula XXXVIII is converted to a 1*H*-imidazo[4,5-*c*]pyridin-6-amine of Formula XXXIX, a subgenus of Formulas I, II, and V, using the methods described in steps (2) through (6) of Reaction Scheme III.

15 In step (7) of Reaction Scheme IV, a 1*H*-imidazo[4,5-*c*]pyridin-6-amine of Formula XXXIX is treated with acid to effect a removal of the Boc group to provide a compound of Formula XL, a subgenus of Formulas I, II, and V. The reaction can be carried out as described in step (7) of Reaction Scheme II.

In step (8) of Reaction Scheme IV, 1*H*-imidazo[4,5-*c*]pyridin-6-amine of Formula XL is further elaborated using the methods described in step (8) of Reaction Scheme II to provide 1*H*-imidazo[4,5-*c*]pyridin-6-amine of Formula XL, a subgenus of Formulas I, II, and V.

20

Reaction Scheme IV



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme V, wherein R, R_{2a}, R_{2b}, R₄, X₁, X', Y, E. and Boc are as defined above; and n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring).

5 In step (1) of Reaction Scheme V, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XX is treated with a Boc-protected diamine of Formula XLII to provide a compound of Formula XLIII. Boc-protected diamines of Formula XLII are available from the corresponding deprotected diamines, which are either commercially available or readily synthesized from amino alcohols of Formula XXI. The
10 Boc protection can be carried out, for example, by treating a diamine such as 1,2-diaminopropane dihydrochloride with one equivalent of di-*tert*-butyl dicarbonate in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The protection reaction can be carried out at a sub-ambient temperature such as 0 °C and allowed to warm to ambient temperature. The reaction shown in step (1) of Reaction Scheme V can be
15 carried out under the conditions described in step (1) of Reaction Scheme I.

In steps (2) and (3) of Reaction Scheme V, a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula XLIII is first reduced to a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XLIV, which is then treated with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLV. Steps (2) and (3) of Reaction Scheme V can be carried out according to the methods described in steps (2) and (3) of Reaction Scheme I.

20 In step (4) of Reaction Scheme V, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLV is brominated using conventional methods to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLVI. The reaction can be carried out by treating a suspension of a compound of Formula XLV in a suitable solvent such as carbon tetrachloride with *N*-bromosuccinimide. The reaction can be carried out at an elevated temperature such as the reflux temperature of the solvent. Optionally, the reaction mixture can be exposed to ultraviolet light.

25 In step (5) of Reaction Scheme V, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLVI is cyclized to provide a compound of Formula XLVII. The reaction can be carried out in two parts (i) by treating a compound

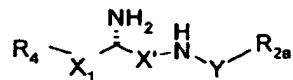
of Formula XLVI with an acid, such as trifluoroacetic acid, to effect removal of the Boc protecting group followed by (ii) treatment with a base to effect intramolecular cyclization by displacement of the bromo group.

In step (6) of Reaction Scheme V, the secondary amine of a compound of Formula XLVII or a salt thereof is converted to an amide, sulfonamide, sulfamide, urea, or tertiary amine of Formula XLVIII using conventional methods. For example, amides, sulfonamides, sulfamides, and ureas can be prepared using the methods described in step (8) of Reaction Scheme II. Compounds of Formula XLVIII where Y is a bond can be prepared by reductive alkylation of the secondary amine of compound of Formula XLVII.

The alkylation can be carried out in two parts by (i) adding an aldehyde or ketone to a solution of a compound of Formula XLVII or a salt thereof in a suitable solvent such as DMF or THF in the presence of a base such as *N,N*-diisopropylethylamine. In part (ii) the reduction can be carried out by adding a suitable reducing agent such as the borane-pyridine complex. Both part (i) and part (ii) can be carried out at ambient temperature.

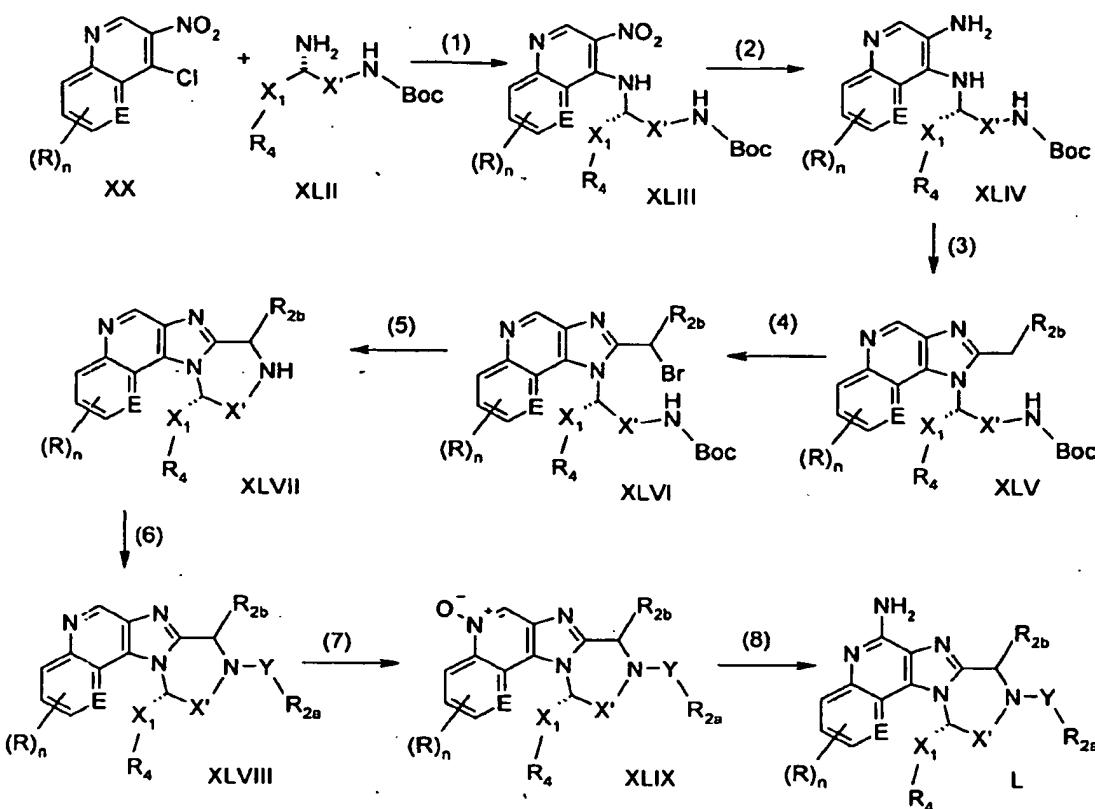
In steps (7) and (8) of Reaction Scheme V, a compound of Formula XLVIII is first oxidized to a *1H*-imidazo[4,5-*c*]quinoline-5*N*-oxide or *1H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XLIX, which is then aminated to provide a *1H*-imidazo[4,5-*c*]quinolin-6-amine or *1H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula L, a subgenus of Formulas I, II, III, and IV. Steps (7) and (8) of Reaction Scheme V can be carried out as described in steps (5) and (6) of Reaction Scheme I.

Alternatively, instead of a Boc-protected diamine of Formula XLII, the reaction sequence shown in Reaction Scheme V can be carried out starting with the reaction of a compound of Formula XX with a compound of Formula



, which can be synthesized from the corresponding diamine using one of the various methods described in step (8) of Reaction Scheme II.

Reaction Scheme V



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme VI, wherein R, R_{1a}, R_{2a}, R_{2b}, R₄, X₁, X', Y, E. and Boc are as defined above; and n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring).

In step (1) of Reaction Scheme VI, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XX is treated with a compound of Formula LI to provide a compound of Formula LII. Compounds of Formula LI can be synthesized from amino alcohols of Formula XXVIII. For example, the primary amino group in a compound of Formula XXVIII can be protected with a suitable protecting group using conventional methods. The hydroxy group can then be converted into a leaving group such as a methanesulfonate. The methanesulfonate group can then be displaced with sodium azide, and the resulting azido substituted compound can be reduced to an amine. The amine can then be treated according to one of the methods described in step (6) of Reaction Scheme V to install a -Y-R_{2a} group. The primary amino group can then be

deprotected according to conventional methods. The reaction in step (1) of Reaction Scheme VI can be carried out using the methods described in step (1) of Reaction Scheme I.

In steps (2) and (3) of Reaction Scheme VI, a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula LII is first reduced to a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula LIII, which is then treated with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LIV. Steps (2) and (3) of Reaction Scheme VI can be carried out according to the methods described in steps (2) and (3) of Reaction Scheme I.

In step (4) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LIV is brominated using conventional methods to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LV. The reaction can be carried out using the methods described in step (4) of Reaction Scheme V.

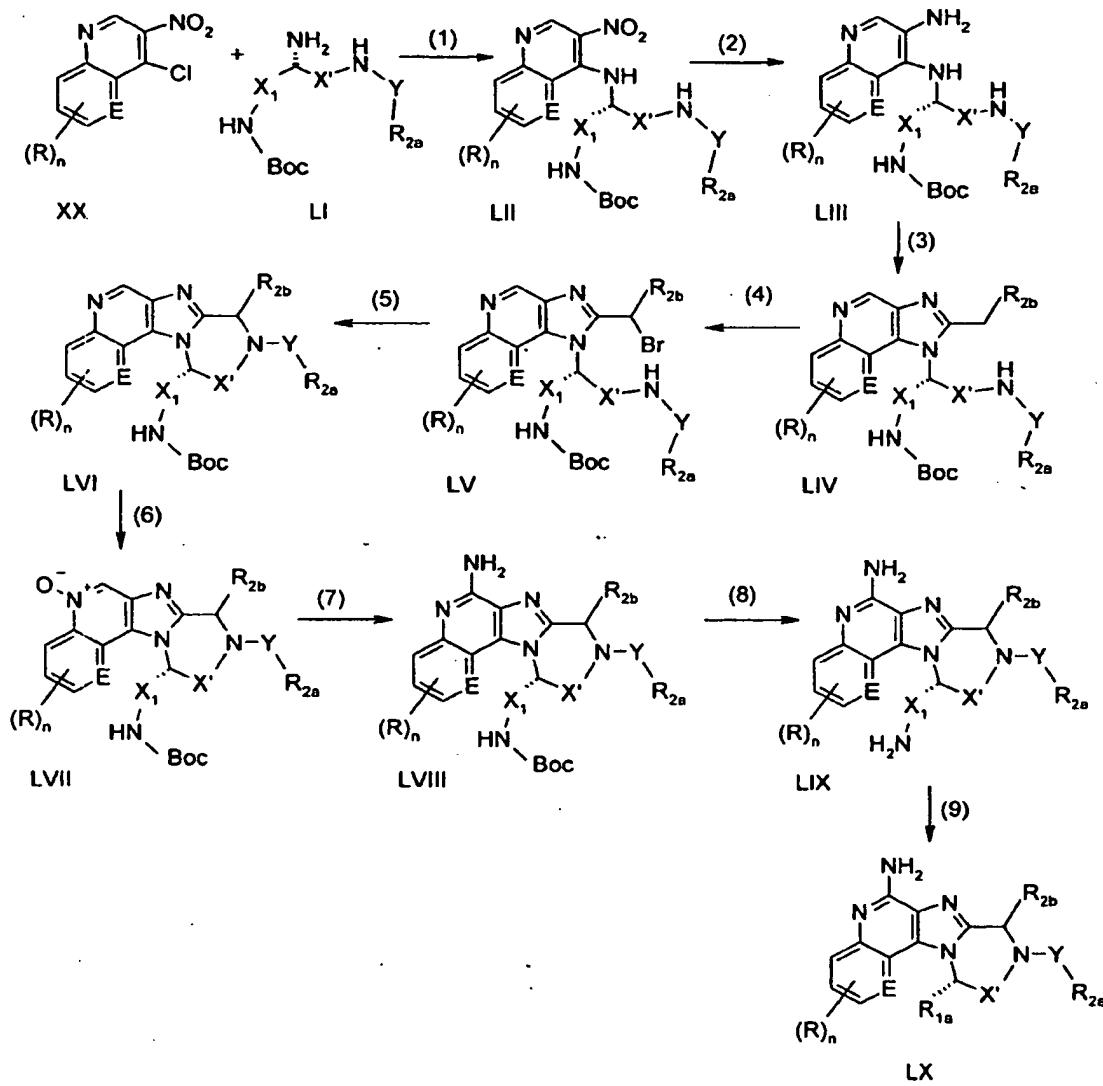
In step (5) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LV is cyclized by an intramolecular displacement of the halogen under basic conditions. The reaction can be carried out by treating a compound of Formula LV with DBU in a suitable solvent such as dichloromethane at ambient temperature.

In steps (6) and (7) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LVI is oxidized and then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula LVIII, a subgenus of Formulas I, II, III, and IV. Steps (6) and (7) of Reaction Scheme VI can be carried out as described in steps (5) and (6) of Reaction Scheme I.

In steps (8) and (9) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula LVIII is deprotected to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula LIX, which is a subgenus of Formulas I, II, III, and IV; and then further elaborated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula LX, a subgenus of Formulas I, II, III, and IV.

Steps (8) and (9) of Reaction Scheme VI can be carried out as described in steps (7) and (8) of Reaction Scheme II.

Reaction Scheme VI

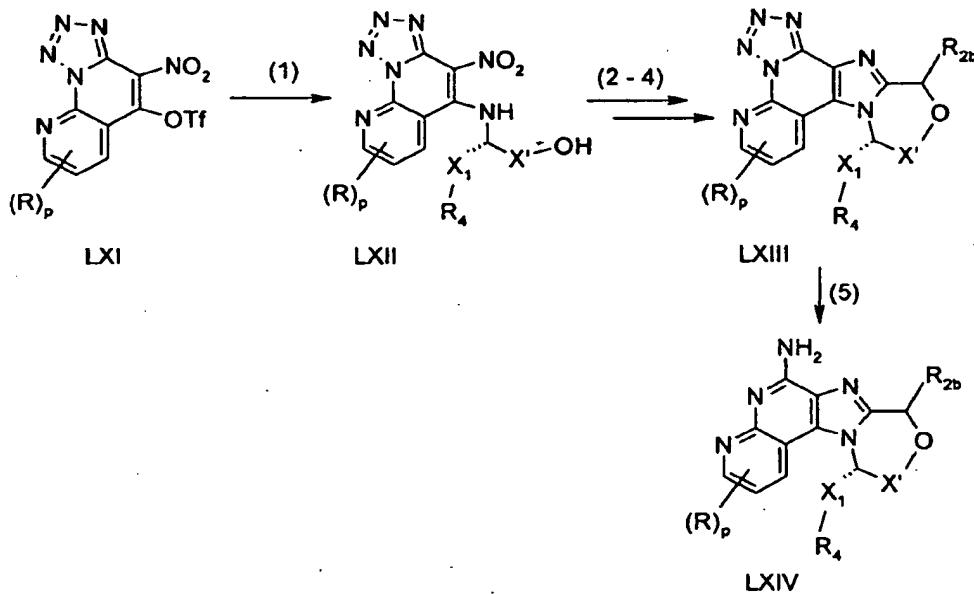


5 For some embodiments, naphthyridines of the invention can be prepared from
tetrazolo compounds of Formulas LXI and LXV according to Reaction Schemes VII and
VIII, wherein R_{2b}, R₄, R, X', X₁, and p are as defined above, and -OTf is a
trifluoromethanesulfonate group. Compounds of Formulas LXI and LXV can be prepared
using known synthetic routes; see, for example, U.S. Patent 6,194,425. The tetrazolo
10 compounds of Formulas LXI and LXV can each be treated with an amino alcohol of

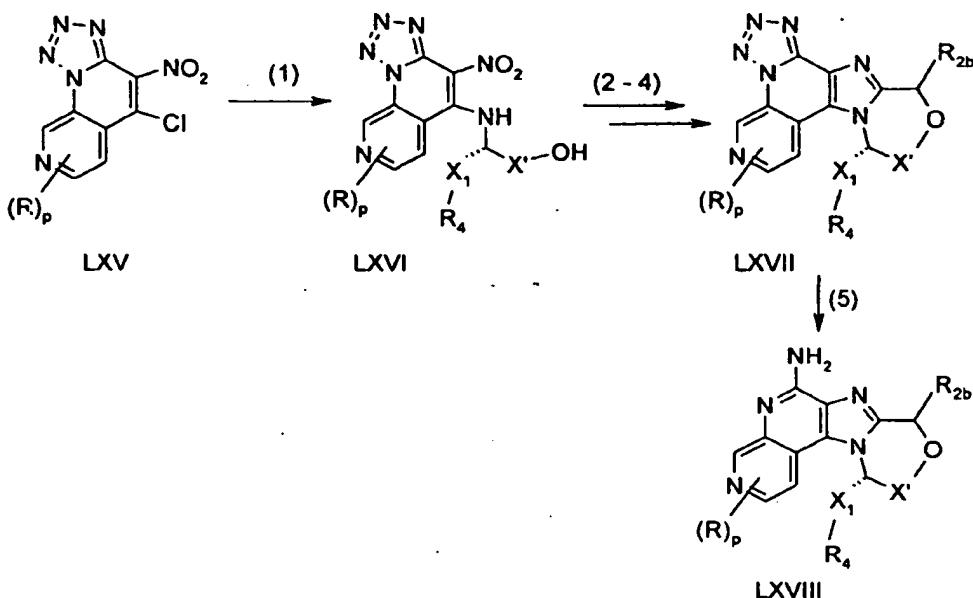
Formula XXI according to the method of step (1) of Reaction Scheme I to provide compounds of Formulas LXII and LXVI, respectively. A tetrazolonaphthyridine of Formula LXII or LXVI can be converted to a compound of Formula LXIII or LXVII using the methods of steps (2) through (4) of Reaction Scheme I.

5 In step (5) of Reaction Scheme VII and VIII, the tetrazolo group is removed from a compound of Formula LXIII or LXVII to provide a 1*H*-imidazo[4,5-*c*]naphthyridin-6-amine of Formula LXIV or Formula LXVIII, which are subgenera of Formulas I and II. Removal of the tetrazolo group can be carried out in two steps by first treating a compound of Formula LXIII or LXVII with triphenylphosphine and then hydrolyzing the 10 resulting intermediate. The reaction conditions described in U.S. Patent 6,194,425 can be used.

Reaction Scheme VII



Reaction Scheme VIII



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme IX, wherein R, R₄, X₁, and X' are as defined above; E is carbon (imidazoquinolines) or nitrogen (imidazonaphthyridines); n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring); and P is a hydroxy protecting group.

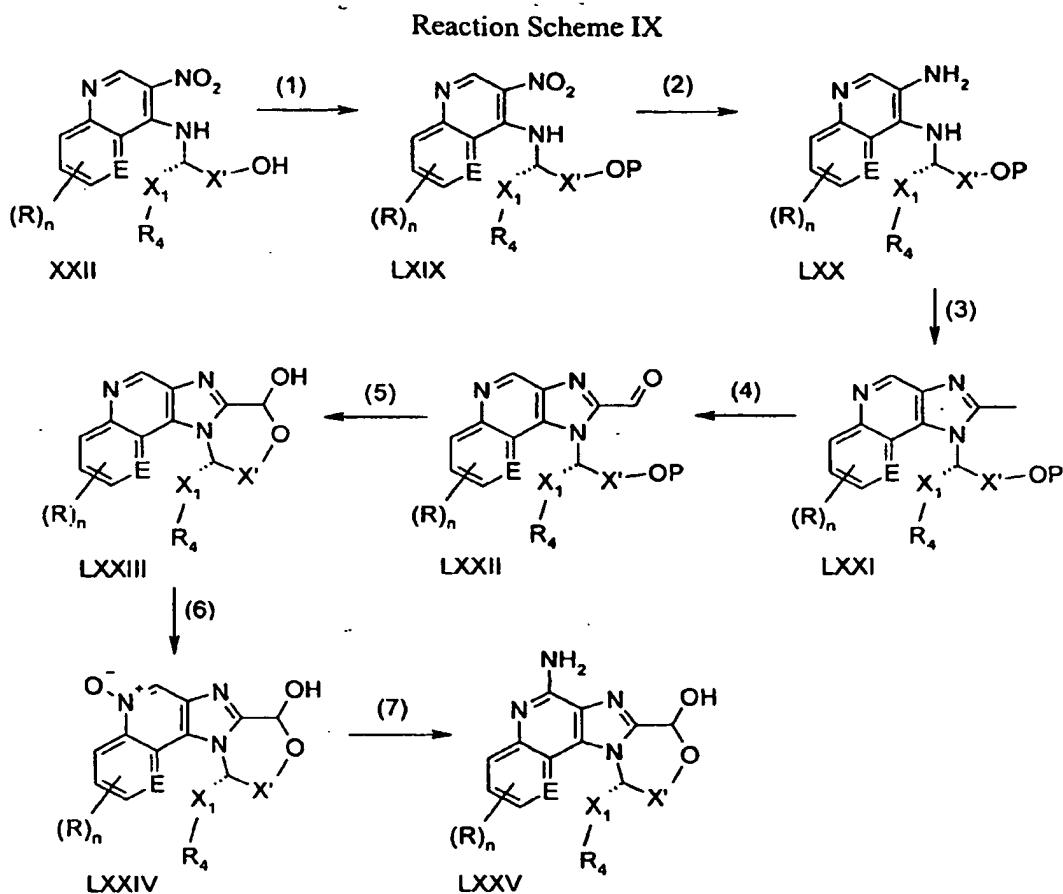
In step (1) of Reaction Scheme IX, the hydroxy group of a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula XXII is protected using conventional techniques to provide a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula LXIX. A number of suitable protecting groups can be used; in particular, protecting groups that would survive the reduction in step (2) are preferred. Suitable protecting groups include but are not limited to silyl groups such as the *tert*-butyl dimethylsilyl group. The reaction can be carried out by treating the hydroxy-substituted compound of Formula XXII with *tert*-butyldimethylsilyl chloride in the presence of a base such as triethylamine and catalytic 4-(dimethylamino)pyridine (DMAP). The reaction can be carried out in a suitable solvent such as dichloromethane or pyridine at an elevated temperature such as the reflux temperature of the solvent or a temperature in the range of 50 °C to 70 °C.

In steps (2) and (3) of Reaction Scheme IX, a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula LXIX is first reduced to a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula LXX, which is then treated with a carboxylic acid equivalent, such as triethyl orthoacetate, to provide a 2-methyl-1*H*-imidazo[4,5-*c*]quinoline or 2-methyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXI. Steps (2) and (3) of Reaction Scheme IX can be carried out according to the methods described in steps (2) and (3) of Reaction Scheme I.

5 In step (4) of Reaction Scheme IX, a 2-methyl-1*H*-imidazo[4,5-*c*]quinoline or 2-methyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXI is oxidized using conventional methods to provide a 1*H*-imidazo[4,5-*c*]quinoline-2-carbaldehyde or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-2-carbaldehyde of Formula LXXII.

10 In step (5) of Reaction Scheme IX, the hydroxy protecting group on a 1*H*-imidazo[4,5-*c*]quinoline-2-carbaldehyde or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-2-carbaldehyde of Formula LXXII is removed and the deprotected compound cyclizes to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXIII. The deprotection reaction can be carried out using a variety of conventional methods, depending on the protecting group used. When P is a silyl group such as *tert*-butyldimethylsilyl, the deprotection can be carried out by adding tetrabutylammonium fluoride to a compound of Formula LXXII in a suitable solvent such as dichloromethane. 15 The reaction can be carried out at a sub-ambient temperature and then warmed to ambient temperature.

20 In steps (6) and (7) of Reaction Scheme IX, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXIII is oxidized and then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula LXXV, a subgenus of Formulas I, II, III, and IV. Steps (6) and (7) of Reaction Scheme IX can be carried out as described in steps (5) and (6) of Reaction Scheme I.



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme X, wherein R, R_4 , X_1 , and X' are as defined above; E is carbon (imidazoquinolines) or nitrogen (imidazonaphthyridines); n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring); R_{2c} is alkyl; and Ms is methanesulfonyl.

In step (1) of Reaction Scheme X, a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XXIII is reacted with an acid chloride of Formula LXXVI to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXVII. The reaction can be carried out by adding an excess of the acid chloride to a solution of a compound of Formula XXIII in a suitable solvent such as dichloromethane or 1,2-dichloroethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at a sub-ambient temperature. Acid chlorides of Formula LXXVI can be prepared from the corresponding alpha hydroxy acids using

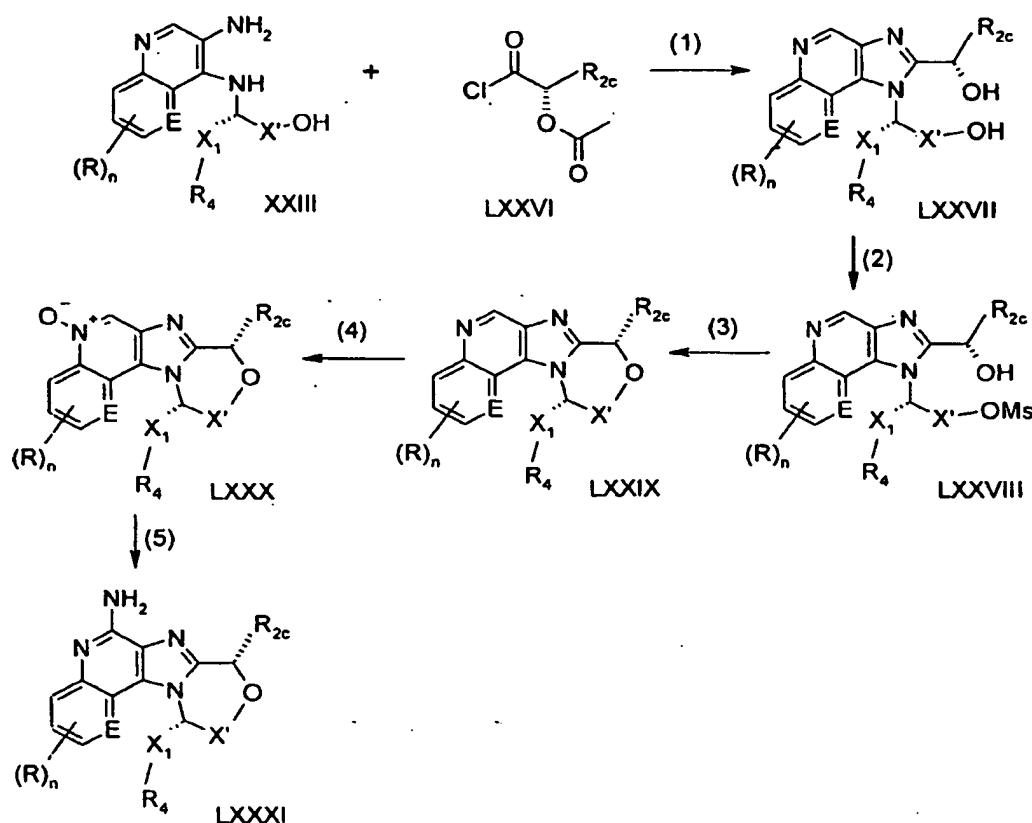
conventional methods. For example, (L)-lactic acid can be treated with acetyl chloride to provide *O*-acetyl-L-lactic acid. This material can then be treated with thionyl chloride to provide the acid chloride. See, Buisson, D. et al., *Tetrahedron Assymetry*, 10, pp 2997-3002 (1999).

5 In step (2) of Reaction Scheme X, the primary alcohol on a *1H*-imidazo[4,5-*c*]quinoline or *1H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXVII is converted to a mesylate. The reaction can be carried out by treating a solution of a compound of Formula LXXVII in a suitable solvent such as dichloromethane with methanesulfonyl chloride in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at 10 ambient temperature or at a sub-ambient temperature.

15 In step (3) of Reaction Scheme X, a *1H*-imidazo[4,5-*c*]quinoline or *1H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXVIII is cyclized by an intramolecular displacement of the mesylate under basic conditions to provide a compound of Formula LXXIX. The reaction can be carried out by adding a base such as potassium *tert*-butoxide to a solution of a compound of Formula LXXVIII in a suitable solvent such as THF. The reaction can be carried out at ambient temperature or at an elevated temperature.

20 In steps (4) and (5) of Reaction Scheme X, a *1H*-imidazo[4,5-*c*]quinoline or *1H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXXIX is oxidized and then aminated to provide a *1H*-imidazo[4,5-*c*]quinolin-6-amine or *1H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula LXXXI, a subgenus of Formulas I, II, III, and IV. Steps (4) and (5) of Reaction Scheme X can be carried out as described in steps (5) and (6) of Reaction Scheme I.

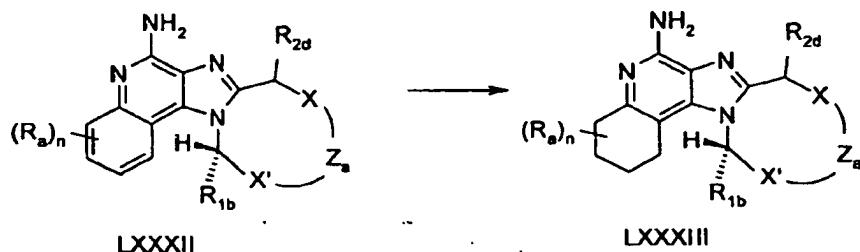
Reaction Scheme X



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme XI, wherein X, X', and n are as defined above; R_a is alkyl, alkoxy, hydroxy, or -N(R₉)₂; Z_a is -O- or -N-(*-Y-R*_{2c}); and R_{1b}, R_{2d}, and R_{2e} are respectively subsets of R₁, R₂, and R_{2a} as defined above that do not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents.

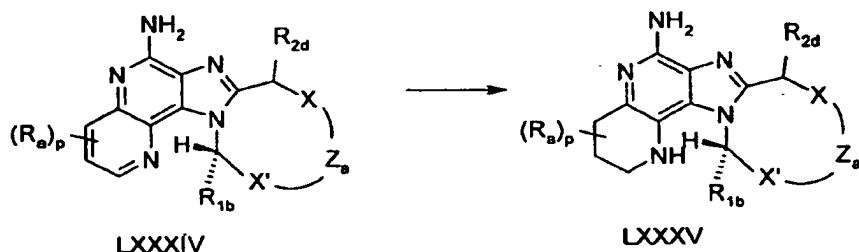
In Reaction Scheme XI, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula LXXXII is reduced to a tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula LXXXIII, a subgenus of Formulas I and II. The reaction can be carried out under heterogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of a compound of Formula LXXXII in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature.

Reaction Scheme XI



The reduction described in Reaction Scheme XI can also be used to prepare a tetrahydro-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula LXXXV, as shown in Reaction Scheme XII, wherein *X*, *X'*, *Z_a*, *p*, *R_a*, *R_{1b}*, and *R_{2d}* are as defined above. The product of Formula LXXXV is a subgenus of Formulas I and II.

Reaction Scheme XII

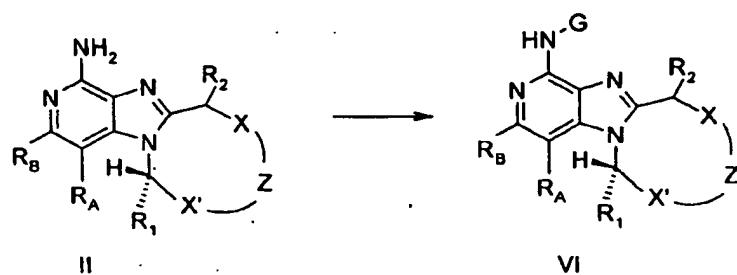


In some embodiments, compounds of the invention can be prepared according to Reaction Scheme XIII wherein *R_A*, *R_B*, *R₁*, *R₂*, *X*, *X'*, *Z*, and *G* are as defined above. The amino group of a compound of Formula II can be converted by conventional methods to a functional group such as an amide, carbamate, urea, amidine, or another hydrolyzable group. A compound of this type can be made by the replacement of a hydrogen atom in an amino group with a group such as -C(O)-R', α -aminoacyl, α -aminoacyl- α -aminoacyl, -C(O)-O-R', -C(O)-N(R'')R', -C(=NY₂)-R', -CH(OH)-C(O)-OY₂, -CH(OC₁₋₄ alkyl)Y₀, -CH₂Y₁, and -CH(CH₃)Y₁; wherein R' and R'' are independently selected from the group consisting of C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, aryl-C₁₋₄ alkylene, heteroaryl-C₁₋₄ alkylene, halo-C₁₋₄ alkylene, halo-C₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃, -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂, with the proviso that R'' can also be hydrogen; each α -aminoacyl is an α -aminoacyl group derived from an α -amino acid selected from the

group consisting of racemic, D-, and L-amino acids; Y₂ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and benzyl; Y₀ is selected from the group consisting of C₁₋₆ alkyl, carboxy-C₁₋₆ alkylenyl, amino-C₁₋₄ alkylenyl, mono-N-C₁₋₆ alkylamino-C₁₋₄ alkylenyl, and di-N,N-C₁₋₆ alkylamino-C₁₋₄ alkylenyl; and Y₁ is selected from the group consisting of mono-N-C₁₋₆ alkylamino, di-N,N-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C₁₋₄ alkylpiperazin-1-yl.

Particularly useful compounds of Formula VI are amides derived from carboxylic acids containing one to ten carbon atoms, amides derived from amino acids, and carbamates containing one to ten carbon atoms. The reaction can be carried out, for example, by combining a compound of Formula II with a chloroformate or acid chloride, such as ethyl chloroformate or acetyl chloride, in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane at ambient temperature.

Reaction Scheme XIII



Methods of installing an R₃ group to provide a compound of Formula III or IV wherein m is 1 are known. See for example, U.S. Patent Application Publication No. 2004/0147543; International Publication Nos. WO 2005/020999, WO 2005/032484, WO 2005/123080, and WO 2006/038923; pending International Application No. PCT/2006/004713; and the references cited therein.

In some embodiments, the R₁ group may be installed or further elaborated using the methods disclosed in pending International Application Nos. PCT/US2005/047258 (Griesgraber) and PCT/US2005/047297 (Griesgraber).

Compounds of the invention can also be prepared using variations of the synthetic routes shown in the Reaction Schemes above that would be apparent to one of skill in the art. For example, a 2,4-dichloro-3-nitropyridine of Formula XXXIII could be used in lieu of a 4-chloro-3-nitroquinoline in Reaction Scheme V and the 6-amine group installed using the method described in Reaction Scheme III; the reduction shown in Reaction

Scheme XII for preparing tetrahydro-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amines could also be used for preparing the other tetrahydronaphthyridine positional isomers; and the strategy used for protecting the alcohol group prior to cyclization that is illustrated in Reaction Scheme IX could also be used in Reaction Schemes I, II, III, IV, VII, and VIII.

5 Compounds of the invention can also be prepared using the synthetic methods described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

10 Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt described above in combination with a pharmaceutically acceptable carrier.

15 The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

20 In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μ g/kg) to about 5 mg/kg, of the compound or salt to the subject.

25 In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 mg/m² to about 5.0 mg/m², computed according to the Dubois method, in which the body surface area of a subject (m²) is computed using the subject's body weight: $m^2 = (\text{wt kg}^{0.425} \times \text{height cm}^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound to provide 30 a dose of from about 0.1 mg/m² to about 2.0 mg/m² to the subject, for example, a dose of from about 0.4 mg/m² to about 1.2 mg/m².

A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon- α (IFN- α) and tumor necrosis factor- α (TNF- α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. The animal to which the compound or salt is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts described herein can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts described herein can also have an effect on the acquired immune response. For example, the production of the T helper type 1 ($T_{H}1$) cytokine IFN- γ may be induced indirectly and the production of the T helper type 2 ($T_{H}2$) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenza virus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas,

Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

5 (c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

10 (d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

15 (e) TH2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

 (f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

20 (g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague,

HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for 5 treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the 10 disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An animal may also be vaccinated by administering an effective amount of a compound or salt described herein, as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt described herein to the animal as a vaccine adjuvant.

15 An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors 20 known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m² to about 5.0 mg/m², (computed according to the Dubois method as described above) although in some 25 embodiments the induction or inhibition of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 mg/m² to about 2.0 mg/m² to the subject, for example, a dose of from about 0.4 mg/m² to about 1.2 mg/m².

30 The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one

or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m² to about 5.0 mg/m², (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt to provide a dose of from about 0.1 mg/m² to about 2.0 mg/m² to the subject, for example, a dose of from about 0.4 mg/m² to about 1.2 mg/m².

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

25

EXAMPLES

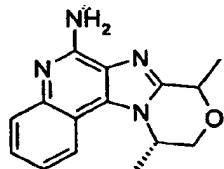
In the examples below automated flash chromatography (AFC) was carried out using a HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA). The eluent used for each purification is given in the example. In some chromatographic separations, the solvent mixture 80/18/2 v/v/v chloroform/methanol/concentrated ammonium hydroxide

(CMA) was used as the polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio.

Example 1

(1*S*)-8,11-Dimethyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

5



Part A

A suspension of 3-chloro-4-nitroquinoline (9.0 g, 43.1 mmol) in 400 mL of dry CH₂Cl₂ was sequentially treated with (2*S*)-2-aminopropan-1-ol (3.7 mL, 47.5 mmol) and triethylamine (12.0 mL, 86.2 mmol), then cooled to 0 °C under an atmosphere of N₂. The reaction was allowed to slowly warm to ambient temperature overnight. The reaction was reduced to ~150 mL of solvent and treated with ~150 mL of H₂O and allowed to stir for ~30 minutes. The yellow precipitate was filtered off and dried to give (2*S*)-2-[(3-nitroquinolin-4-yl)amino]propan-1-ol (10.50 g) as a bright yellow solid.

15

Part B

A pressure bottle was charged with platinum on carbon (5%, 0.27 g) followed by (2*S*)-2-[(3-nitroquinolin-4-yl)amino]propan-1-ol (1.11 g, 4.49 mmol) dissolved in 200 mL of toluene. The reaction mixture was shaken under H₂ at 48 PSI (3.3 × 10⁵ Pa). The next day the reaction was filtered through a pad of CELITE filter agent and rinsed with toluene. The solvent was removed under reduced pressure to give (2*S*)-2-[(3-aminoquinolin-4-yl)amino]propan-1-ol (1.13 g) as an orange oil.

Part C

A suspension of (2*S*)-2-[(3-aminoquinolin-4-yl)amino]propan-1-ol (0.98 g, 4.49 mmol) in 50 mL of toluene was treated with triethyl orthopropioate (1.1 mL, 5.39 mmol) and pyridine HCl (52 mg, 0.45 mmol), and heated to 90 °C under an atmosphere of N₂. After ~20 hours, the reaction was allowed to cool back to ambient temperature and the solvent was removed under reduced pressure to give an orange solid. Chromatography (AFC, SiO₂, 20-40% CMA/CHCl₃) gave (2*S*)-2-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propan-1-ol (0.70 g) as a white solid.

Part D

(2*S*)-2-(2-Ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propan-1-ol (0.50 g, 1.96 mmol) was suspended in 20 mL of CCl₄ under an atmosphere of N₂. The mixture was treated with *N*-bromosuccinimide (0.35 g, 1.96 mmol), heated to reflux, and irradiated with a sunlamp. After ~20 hours the reaction was allowed to cool to ambient temperature, then it was partitioned between CH₂Cl₂ and saturated NaHCO₃ solution. The layers were separated; the organic layer was washed sequentially with saturated NaHCO₃ solution and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a brown foam. Chromatography (AFC, SiO₂, 0-15% CMA/CHCl₃) gave (11*S*)-8,11-dimethyl-10,11-dihydro-8*H*-[1;4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (80 mg) as a light yellow solid.

Part E

A solution of (11*S*)-8,11-dimethyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (80 mg, 0.316 mmol) and 5 mL of CHCl₃ was treated with MCPBA (*meta*-chloroperoxybenzoic acid) (93 mg, 77% max). After 18 hours, the reaction was treated with ~10 mL of CHCl₃ and 5 mL of 2% Na₂CO₃ solution and the layers were separated. The aqueous layer was extracted with CHCl₃ (5 x 10 mL). The organic layers were combined then washed with brine, dried over Na₂SO₄, filtered, and concentrated to give (11*S*)-8,11-dimethyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide (85 mg) as a light yellow solid.

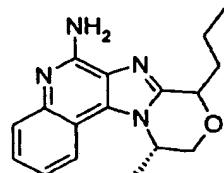
Part F

A solution of (11*S*)-8,11-dimethyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline 5-oxide (85 mg, 0.316 mmol) in 5 mL of CH₂Cl₂ was treated with 1 mL of concentrated aqueous ammonium hydroxide and stirred vigorously. *p*-Toluenesulfonyl chloride (60 mg, 0.316 mmol) was added in one portion. The following day the reaction was treated with 5 mL of H₂O and 10 mL of CH₂Cl₂, and the layers were separated. The organic layer was washed sequentially with saturated NaHCO₃ solution (2x) and brine, dried over Na₂SO₄, filtered, and concentrated to give a light yellow solid. Chromatography (AFC, SiO₂, 0-20% CMA/CHCl₃) afforded (11*S*)-8,11-dimethyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (25 mg) as a white solid, m.p. 218 - 223°C.

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.44 (m, 1H), 7.28 (m, 1H), 6.58 (s, 2H), 5.29 (m, 1H), 5.07 (m, 1H), 4.35 (m, 1H), 3.87 (m, 1H), 1.61 (d, *J* = 6.9 Hz, 3H), 1.56 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (175 MHz, DMSO-*d*₆) δ 152.3, 149.6, 145.0, 131.6, 127.0, 126.9, 126.6, 121.7, 120.8, 115.0, 69.5, 63.7, 50.7, 20.0, 19.2; HRMS (ESI) calcd for C₁₅H₁₆N₄O 269.1402, found 269.1393.

Example 2

(11*S*)-11-Methyl-8-propyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

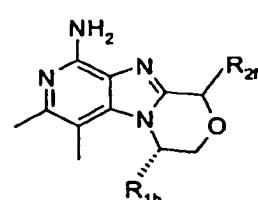
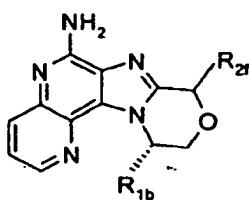
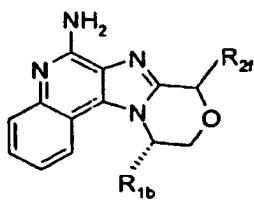


The title compound was prepared from (2*S*)-2-[(3-aminoquinolin-4-yl)amino]propan-1-ol and trimethyl orthovalerate following Parts C through F listed for the preparation of Example 1 with the following modifications. Chromatography (AFC, SiO₂, 10-30% CMA/CHCl₃) in Part C afforded the desired product, Part D required two chromatographic purifications, and the product in Part F was triturated in 10 mL of ether after chromatography. The solid was then isolated by filtration to give (11*S*)-11-methyl-8-propyl-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (4 mg) as a white solid, m.p. 243 - 268 °C.

¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.52 (m, 1H), 7.33 (m, 1H), 5.37 (s, 2H), 5.13 (m, 1H), 4.92 (m, 1H), 4.31 (dd, *J* = 11.9, 3.1 Hz, 1H), 3.89 (m, 1H), 2.03 (m, 2H), 1.73 (d, *J* = 6.3 Hz, 3H), 1.68 (m, 2H), 1.05 (t, *J* = 7.5 Hz, 3H); HRMS (ESI) calcd for C₁₇H₂₀N₄O 297.1715, found 297.1714.297.1714

Exemplary Compounds

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIa, IVa, or Va) and the following R_{1b} and R_{2f} substituents, wherein each line of the table is matched with Formula IIIa, IVa, or Va to represent a specific embodiment of the invention.



R _{1b}	R _{2f}
methyl	methyl
methyl	ethyl
methyl	propyl
methyl	methoxymethyl
isopropyl	methyl
isopropyl	ethyl
isopropyl	propyl
isopropyl	methoxymethyl
1-fluoro-1-methylethyl	methyl
1-fluoro-1-methylethyl	ethyl
1-fluoro-1-methylethyl	propyl
1-fluoro-1-methylethyl	methoxymethyl
1-hydroxy-1-methylethyl	methyl
1-hydroxy-1-methylethyl	ethyl
1-hydroxy-1-methylethyl	propyl
1-hydroxy-1-methylethyl	methoxymethyl
phenyl	methyl
phenyl	ethyl
phenyl	propyl
phenyl	methoxymethyl
benzyl	methyl
benzyl	ethyl
benzyl	propyl
benzyl	methoxymethyl

1-hydroxyethyl	methyl
1-hydroxyethyl	ethyl
1-hydroxyethyl	propyl
1-hydroxyethyl	methoxymethyl
tetrahydro-2H-pyran-4-yl	methyl
tetrahydro-2H-pyran-4-yl	ethyl
tetrahydro-2H-pyran-4-yl	propyl
tetrahydro-2H-pyran-4-yl	methoxymethyl

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α in human cells when tested using one of the methods described below.

5

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN- α and TNF- α , respectively) secreted into culture media as described by Testerman et. al. in 10 "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using 15 HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) 20 centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4×10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 µM.

5 Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 µM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then 10 added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 µM). The final concentration of PBMC suspension is 2 x 10⁶ cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

15 Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

20 Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and 25 read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

30 In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve.

The reference compound used is 2-[4-amino-2-ethoxymethyl]-6,7,8,9-tetrahydro- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μ molar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

CYTOKINE INDUCTION IN HUMAN CELLS

(High Throughput Screen)

The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient

medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4×10^6 cells/mL in RPMI complete (2-fold the final cell density). The PBMC suspension is added to 96-well flat bottom sterile tissue culture plates.

Compound Preparation

5 The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014 μ M. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) 10 on each plate. The solution of test compound is added at 7.5 mM to the first well of a dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028 μ M) than the final tested concentration range.

15 Incubation

Compound solution is then added to the wells containing the PBMC suspension bringing the test compound concentrations to the desired range (usually 30 - 0.014 μ M) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then 20 incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4°C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. 25 (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70°C until analysis.

Interferon- α and Tumor Necrosis Factor- α Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human 30 TNF- α and human IFN- α that have been pre-coated on specific spots. Each well contains four spots: one human TNF- α capture antibody (MSD) spot, one human IFN- α capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine

serum albumin spots. The human TNF- α capture and detection antibody pair is from MesoScale Discovery. The human IFN- α multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN- α subtypes except IFN- α F (IFNA21). Standards consist of recombinant human TNF- α (R&D Systems, Minneapolis, MN) and IFN- α (PBL Biomedical Laboratories). Samples and separate standards are added at the time of analysis to each MSD plate. Two human IFN- α detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the IFN- α concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF- α or IFN- α (y-axis) as a function of compound concentration (x-axis).

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates. Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN- α , TNF- α) are reported. Data from plates with scaling factors outside the above mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No.

5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

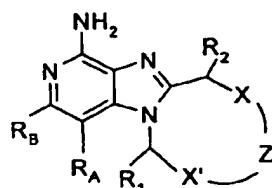
A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a 5 single adjustment ratio to decrease experiment-to-experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the 10 sum of the median dose values from an average of previous experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The 15 minimum effective concentration (μ molar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

20 The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited 25 by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the Formula I:



I

wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

10 X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

15 Z is selected from the group consisting of -O- and -N(-Y-R_{2a})-;

R₁ is selected from the group consisting of:

- X₁-R₄,
- X₁-Y'-R₄,
- X₁-Y'-X"-Y'-R₄, and

20 -X₁-R₅;

R₂ is selected from the group consisting of hydroxy, alkoxy, alkyl, and alkenyl wherein the alkyl group can be unsubstituted or substituted by one more substituents independently selected from the group consisting of alkoxy, amino, hydroxy, and methanesulfonylamino;

25 R_A and R_B are each independently selected from the group consisting of:

- hydrogen,
- halogen,
- alkyl,
- alkenyl,

alkoxy,
alkylthio, and
-N(R₉)₂;

or when taken together, R_A and R_B form a fused aryl or heteroaryl ring
5 containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group;
or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S,
10 and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
15 alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R₉)₂;

20 R₃ is selected from the group consisting of:
-Z'-R₄,
-Z'-X"-R₄,
-Z'-X"-Y'-R₄,
-Z'-X"-Y'-X"-Y'-R₄, and
25 -Z'-X"-R₅;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

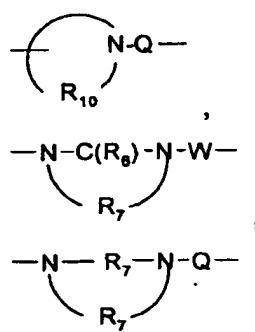
30 X" is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclene and optionally interrupted by one or more -O- groups;

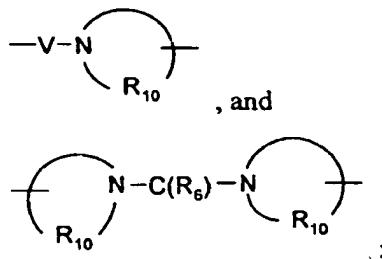
Y is selected from the group consisting of:

- a bond,
- S(O)₂-,
- S(O)₂-N(R₈)-,
- C(R₆)-,
- C(R₆)-N(R₈)-,
- C(R₆)-N(R₈)-C(R₆)-,
- C(R₆)-N(R₈)-S(O)₂-, and
- C(R₆)-O-;

10 Y' is selected from the group consisting of:

- O-,
- S(O)₀₋₂-,
- S(O)₂-N(R₈)-,
- C(R₆)-,
- C(R₆)-O-,
- O-C(R₆)-,
- O-C(O)-O-,
- N(R₈)-Q-,
- C(R₆)-N(R₈)-,
- O-C(R₆)-N(R₈)-,
- C(R₆)-N(OR₉)-,
- O-N(R₈)-Q-,
- O-N=C(R₄)-,
- C(=N-O-R₈)-,
- 25 -CH(-N(-O-R₈)-Q-R₄)-,



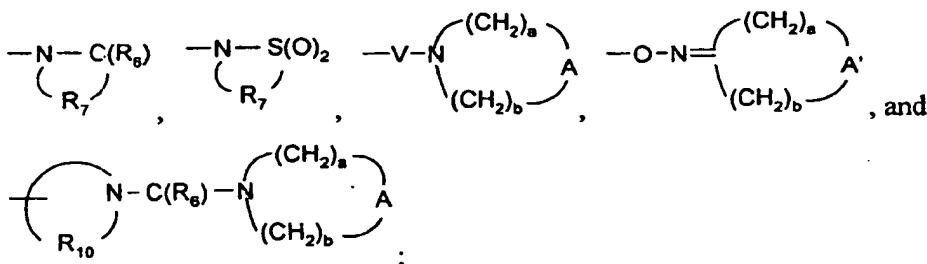


Z' is a bond or -O-;

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl,
 5 arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,
 heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,
 alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,
 heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups
 can be unsubstituted or substituted by one or more substituents independently selected
 10 from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy;
 alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto;
 cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy;
 heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;
 (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;
 15 and, in the case of aryl, methylenedioxy;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl,
 arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,
 heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,
 alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,
 20 heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups
 can be unsubstituted or substituted by one or more substituents independently selected
 from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen;
 nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl;
 heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;
 25 (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,
 oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of $=\text{O}$ and $=\text{S}$;

R_7 is C_{2-7} alkylene;

5 R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylene, C_{1-10} alkoxy- C_{1-10} alkylene, aryl- C_{1-10} alkylene, and heteroaryl- C_{1-10} alkylene;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

10 A is selected from the group consisting of $-\text{CH}_2-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S(O)}_{0-2}-$, and $-\text{N}(-\text{Q-R}_4)-$;

A' is selected from the group consisting of $-\text{O}-$, $-\text{S(O)}_{0-2}-$, $-\text{N}(-\text{Q-R}_4)-$, and $-\text{CH}_2-$;

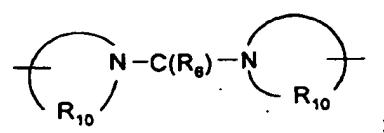
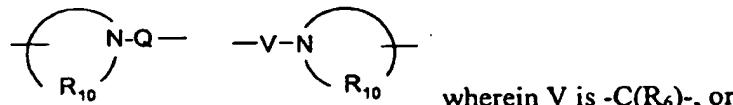
Q is selected from the group consisting of a bond, $-\text{C}(\text{R}_6)-$, $-\text{C}(\text{R}_6)\text{C}(\text{R}_6)-$, $-\text{S(O)}_{0-2}-$, $-\text{C}(\text{R}_6)\text{-N}(\text{R}_8)\text{-W-}$, $-\text{S(O)}_2\text{-N}(\text{R}_8)-$, $-\text{C}(\text{R}_6)\text{-O-}$, $-\text{C}(\text{R}_6)\text{-S-}$, and $-\text{C}(\text{R}_6)\text{-N}(\text{OR}_9)-$;

15 V is selected from the group consisting of $-\text{C}(\text{R}_6)-$, $-\text{O-C}(\text{R}_6)-$, $-\text{N}(\text{R}_8)\text{-C}(\text{R}_6)-$, and $-\text{S(O)}_2-$;

W is selected from the group consisting of a bond, $-\text{C}(\text{O})-$, and $-\text{S(O)}_2-$; and

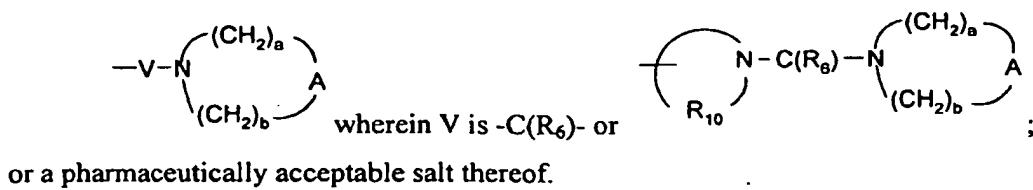
a and b are independently integers from 1 to 6 with the proviso that $\text{a} + \text{b}$ is ≤ 7 ; with the proviso that X_1 can also be a bond when:

20 Y' is bonded to X_1 and Y' is $-\text{C}(\text{R}_6)-$, $-\text{C}(\text{R}_6)\text{-O-}$, $-\text{C}(\text{R}_6)\text{-N}(\text{R}_8)-$, $-\text{C}(\text{R}_6)\text{-N}(\text{OR}_9)-$, $-\text{C}(\text{R}_6)\text{-N}(\text{O-R}_9)-$, $-\text{C}(\text{=N-O-R}_8)-$, $-\text{CH}(-\text{N}(-\text{O-R}_8)\text{-Q-R}_4)-$,



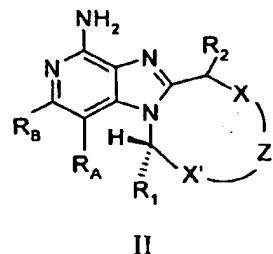
R_4 is bonded to X_1 and R_4 is other than hydrogen; or

25 R_5 is bonded to X_1 and R_5 is



2. A compound of the Formula II:

5



wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

15 X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_{2a})-;

R₁ is selected from the group consisting of:

-X₁-R₄,

20 -X₁-Y'-R₄,

-X₁-Y'-X"-Y'-R₄, and

-X₁-R₅;

R₂ is selected from the group consisting of hydroxy, alkoxy, alkyl, and alkenyl wherein the alkyl group can be unsubstituted or substituted by one more substituents independently selected from the group consisting of alkoxy, amino, hydroxy, and methanesulfonylamino;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

5 alkaryl,

alkoxy,

alkylthio, and

-N(R₉)₂;

or when taken together, R_A and R_B form a fused aryl or heteroaryl ring

10 containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, 15 and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

20 alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

25 R₃ is selected from the group consisting of:

-Z'-R₄,

-Z'-X"-R₄,

-Z'-X"-Y'-R₄,

-Z'-X"-Y'-X"-Y'-R₄, and

30 -Z'-X"-R₅;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

X" is selected from the group consisting of alkylene, alkenylene, alkynylene, 5 arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

a bond,

10 -S(O)₂-,

-S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-N(R₈)-,

-C(R₆)-N(R₈)-C(R₆)-,

15 -C(R₆)-N(R₈)-S(O)₂-, and

-C(R₆)-O-;

Y' is selected from the group consisting of:

-O-,

-S(O)₀₋₂-,

20 -S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-O-,

-O-C(R₆)-,

-O-C(O)-O-,

25 -N(R₈)-Q-,

-C(R₆)-N(R₈)-,

-O-C(R₆)-N(R₈)-,

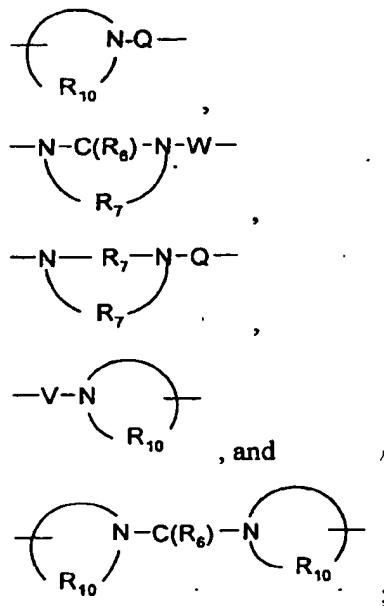
-C(R₆)-N(OR₉)-,

-O-N(R₈)-Q-,

30 -O-N=C(R₄)-,

-C(=N-O-R₈)-,

-CH(-N(-O-R₈)-Q-R₄)-,



5

Z' is a bond or $-O-$;

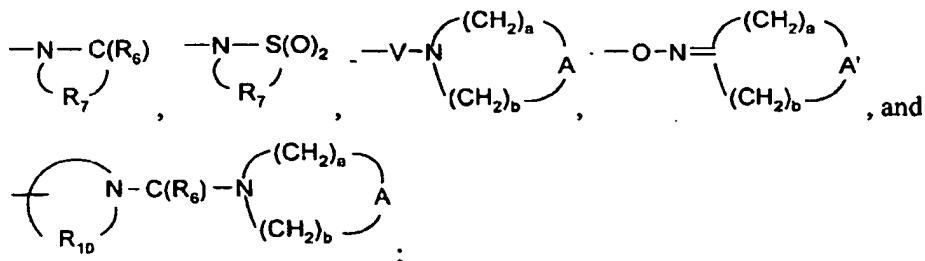
R_{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected

from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,

5 oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

10 R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylene, C_{1-10} alkoxy- C_{1-10} alkylene, aryl- C_{1-10} alkylene, and heteroaryl- C_{1-10} alkylene;

15 R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, $-O-$, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(-Q-R_4)-$;

A' is selected from the group consisting of $-O-$, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, 20 $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

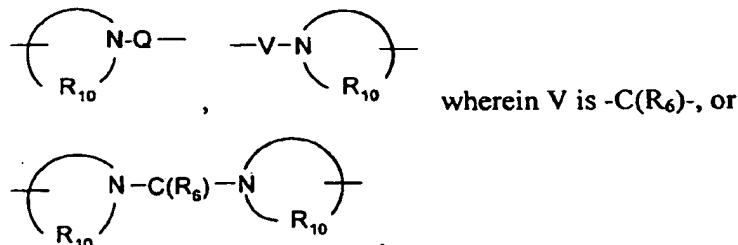
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

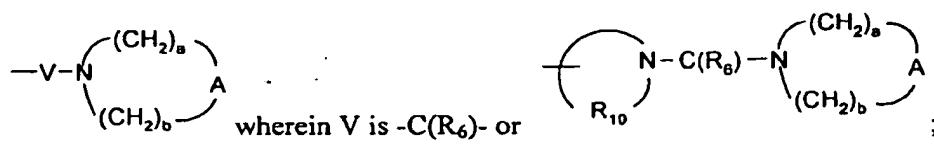
25 with the proviso that X_1 can also be a bond when:

Y' is bonded to X_1 and Y' is $-C(R_6)-$, $-C(R_6)-O-$, $-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,



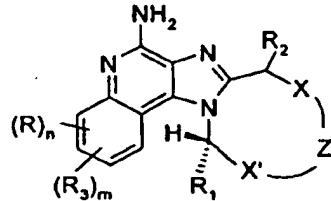
R_4 is bonded to X_1 and R_4 is other than hydrogen; or
 R_5 is bonded to X_1 and R_5 is

5



or a pharmaceutically acceptable salt thereof.

3. A compound of the Formula III:



10

III

wherein:

X is a bond or a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

15

X' is a straight or branched chain C_{1-8} alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

20

Z is selected from the group consisting of $-O-$ and $-N(-Y-R_{2a})-$;

R_1 is selected from the group consisting of:

$-X_1-R_4$,

$-X_1-Y'-R_4$,

-X₁-Y'-X"-Y'-R₄, and

-X₁-R₅;

R₂ is selected from the group consisting of hydroxy, alkoxy, alkyl, and alkenyl wherein the alkyl group can be unsubstituted or substituted by one more substituents
5 independently selected from the group consisting of alkoxy, amino, hydroxy, and methanesulfonylamino;

R is selected from the group consisting of:

halogen,

hydroxy,

10 alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and ..

15 -N(R₉)₂;

R₃ is selected from the group consisting of:

-Z'-R₄,

-Z'-X"-R₄,

-Z'-X"-Y'-R₄,

20 -Z'-X"-Y'-X"-Y'-R₄, and

-Z'-X"-R₅;

n is an integer from 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the
25 alkylene and alkenylene are optionally interrupted by one or more -O- groups, and
optionally substituted by a hydroxy or methoxy group;

X" is selected from the group consisting of alkylene, alkenylene, alkynylene,
arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and
alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or
30 heterocyclene and optionally interrupted by one or more -O- groups;

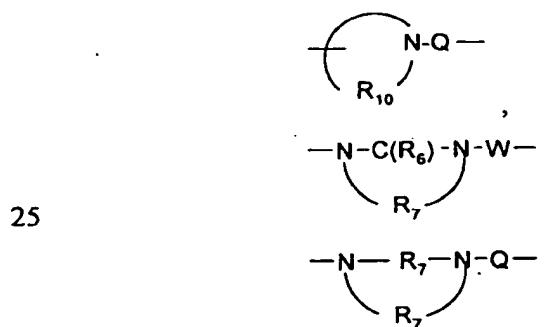
Y is selected from the group consisting of:

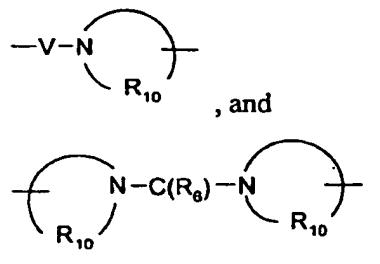
a bond,

5
 -S(O)₂-,
 -S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-N(R₈)-,
 -C(R₆)-N(R₈)-C(R₆)-,
 -C(R₆)-N(R₈)-S(O)₂-, and
 -C(R₆)-O-;

Y' is selected from the group consisting of:

10
 -O-,
 -S(O)₀₋₂-,
 -S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-O-,
 -O-C(R₆)-,
 15
 -O-C(O)-O-,
 -N(R₈)-Q-,
 -C(R₆)-N(R₈)-,
 -O-C(R₆)-N(R₈)-,
 -C(R₆)-N(OR₉)-,
 20
 -O-N(R₈)-Q-,
 -O-N=C(R₄)-,
 -C(=N-O-R₈)-,
 -CH(-N(-O-R₈)-Q-R₄)-,



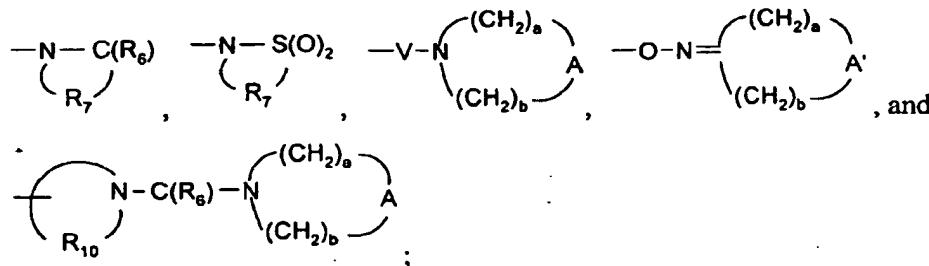


Z' is a bond or -O-;

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, 5 arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected 10 from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxy carbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; 15 and, in the case of aryl, methylenedioxy;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected 20 from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, 25 oxo;

R_5 is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

5 R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, hydroxy-C₁₋₁₀ alklenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alklenyl, aryl-C₁₋₁₀ alklenyl, and heteroaryl-C₁₋₁₀ alklenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

10 A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and -N(-Q-R₄)-;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-,

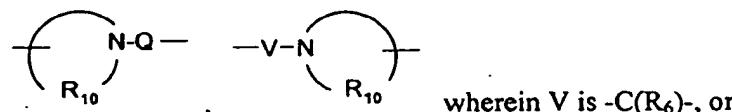
Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, -C(R₆)-S-, and -C(R₆)-N(OR₉)-;

15 V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-,

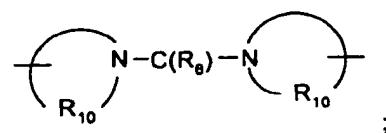
W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-, and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; with the proviso that X₁ can also be a bond when:

20 Y' is bonded to X₁ and Y' is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,

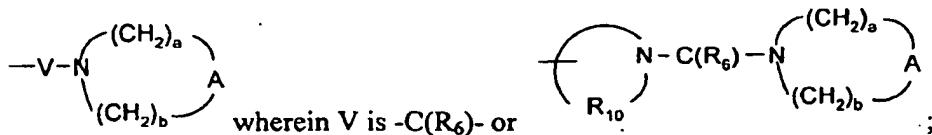


wherein V is -C(R₆)-, or



R₄ is bonded to X₁ and R₄ is other than hydrogen; or

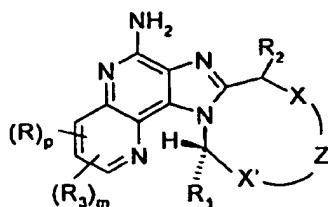
25 R₅ is bonded to X₁ and R₅ is



or a pharmaceutically acceptable salt thereof.

4. A compound of the Formula IV:

5



IV

wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

15 X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_{2a})-;

R₁ is selected from the group consisting of:

-X₁-R₄,

20 -X₁-Y'-R₄,

-X₁-Y'-X"-Y'-R₄, and

-X₁-R₅;

R₂ is selected from the group consisting of hydroxy, alkoxy, alkyl, and alkenyl wherein the alkyl group can be unsubstituted or substituted by one more substituents independently selected from the group consisting of alkoxy, amino, hydroxy, and methanesulfonylamino;

R is selected from the group consisting of:

- halogen,
- hydroxy,
- alkyl,
- 5 alkenyl,
- haloalkyl,
- alkoxy,
- alkylthio, and
- N(R₉)₂;

10 R₃ is selected from the group consisting of:

- Z'-R₄,
- Z'-X"-R₄,
- Z'-X"-Y'-R₄,
- Z'-X"-Y'-X"-Y'-R₄, and
- 15 -Z'-X"-R₅;

p is an integer from 0 to 3;

m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and
20 optionally substituted by a hydroxy or methoxy group;

X" is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

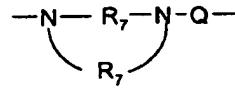
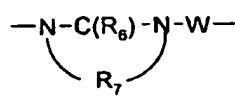
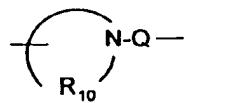
25 Y is selected from the group consisting of:

- a bond,
- S(O)₂-,
- S(O)₂-N(R₈)-,
- C(R₆)-,
- 30 -C(R₆)-N(R₈)-,
- C(R₆)-N(R₈)-C(R₆)-,
- C(R₆)-N(R₈)-S(O)₂-, and

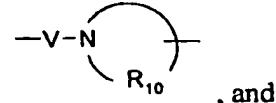
-C(R₆)-O-;

Y' is selected from the group consisting of:

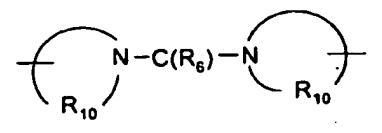
- O-,
- S(O)₀₋₂₋,
- 5 -S(O)₂-N(R₈)-,
- C(R₆)-,
- C(R₆)-O-,
- O-C(R₆)-,
- O-C(O)-O-,
- 10 -N(R₈)-Q-,
- C(R₆)-N(R₈)-,
- O-C(R₆)-N(R₈)-,
- C(R₆)-N(OR₉)-,
- O-N(R₈)-Q-,
- 15 -O-N=C(R₄)-,
- C(=N-O-R₈)-,
- CH(-N(-O-R₈)-Q-R₄)-,



20



, and

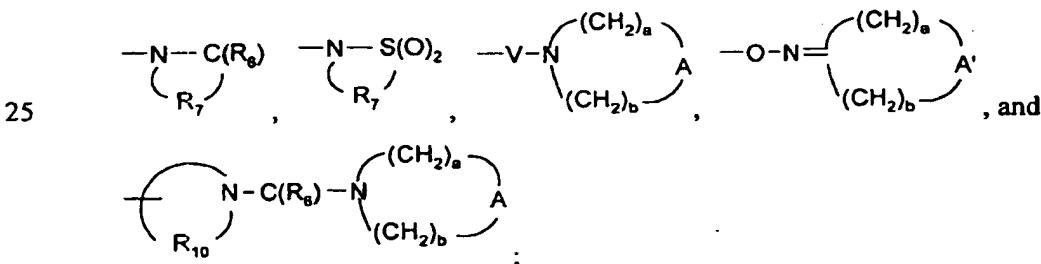


Z' is a bond or -O-;

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylkyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylkyl, heteroaryloxyalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylkyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylkyl, heteroaryloxyalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, aryl- C_{1-10} alkylenyl, and heteroaryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

5 R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, $-O-$, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(-Q-R_4)-$;

A' is selected from the group consisting of $-O-$, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$,

10 $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

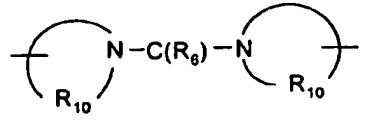
a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ;

15 with the proviso that X_1 can also be a bond when:

Y' is bonded to X_1 and Y' is $-C(R_6)-$, $-C(R_6)-O-$, $-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,

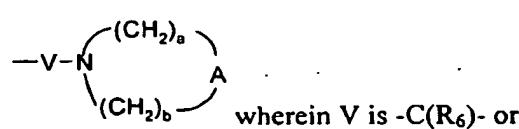


wherein V is $-C(R_6)-$, or

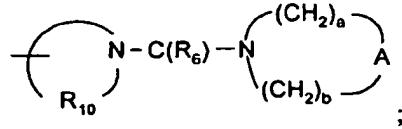


20 R_4 is bonded to X_1 and R_4 is other than hydrogen; or

R_5 is bonded to X_1 and R_5 is

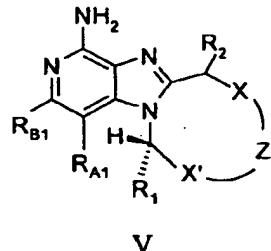


wherein V is $-C(R_6)-$ or



or a pharmaceutically acceptable salt thereof.

25 5. A compound of the Formula V:



wherein:

5 X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

10 X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

15 X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R_{2a})-;

R₁ is selected from the group consisting of:

-X₁-R₄,

15 -X₁-Y'-R₄,

-X₁-Y'-X"-Y'-R₄, and

-X₁-R₅;

20 R₂ is selected from the group consisting of hydroxy, alkoxy, alkyl, and alkenyl wherein the alkyl group can be unsubstituted or substituted by one more substituents independently selected from the group consisting of alkoxy, amino, hydroxy, and methanesulfonylamino;

25 R_{A1} and R_{B1} are each independently selected from the group consisting of:
hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and

-N(R₉)₂;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

5 X" is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

10 a bond,

-S(O)₂-,

-S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-N(R₈)-,

15 -C(R₆)-N(R₈)-C(R₆)-,

-C(R₆)-N(R₈)-S(O)₂-, and

-C(R₆)-O-;

Y' is selected from the group consisting of:

-O-,

20 -S(O)₀₋₂₋,

-S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-O-,

-O-C(R₆)-,

25 -O-C(O)-O-,

-N(R₈)-Q-,

-C(R₆)-N(R₈)-,

-O-C(R₆)-N(R₈)-,

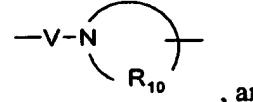
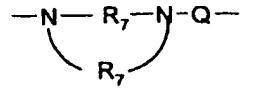
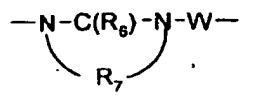
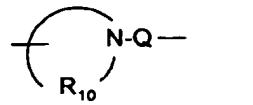
-C(R₆)-N(OR₉)-,

30 -O-N(R₈)-Q-,

-O-N=C(R₄)-,

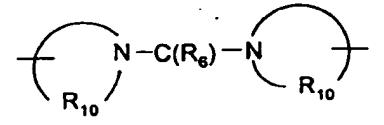
-C(=N-O-R₈)-,

-CH(-N(-O-R₈)-Q-R₄)-,



5

, and



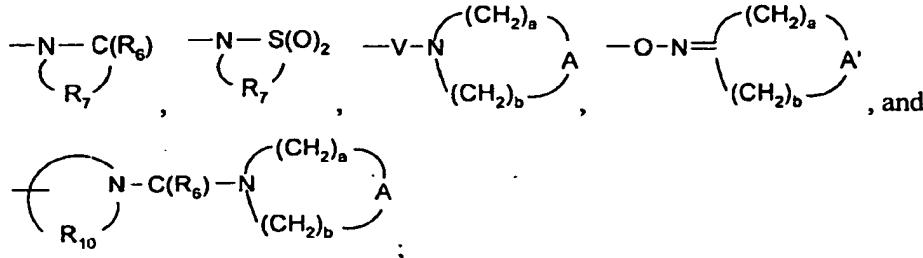
;

R_{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxy carbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected

from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,
 5 oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

10 R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylene, C_{1-10} alkoxy- C_{1-10} alkylene, aryl- C_{1-10} alkylene, and heteroaryl- C_{1-10} alkylene;

15 R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, $-O-$, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(-Q-R_4)-$;

A' is selected from the group consisting of $-O-$, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

20 Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_{0-2}-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

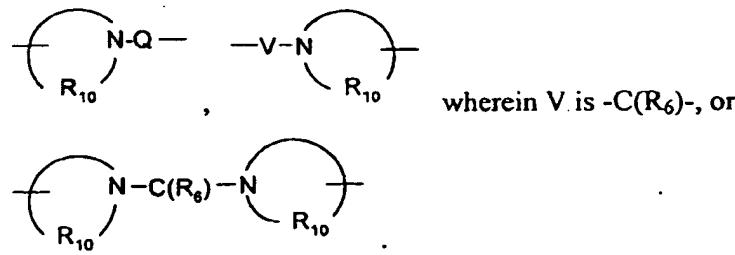
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

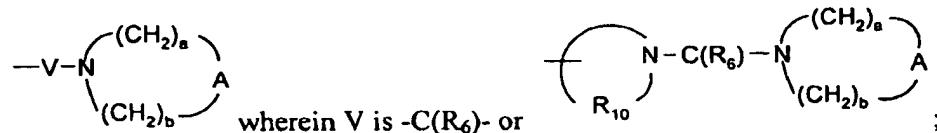
25 with the proviso that X_1 can also be a bond when:

Y' is bonded to X_1 and Y' is $-C(R_6)-$, $-C(R_6)-O-$, $-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,



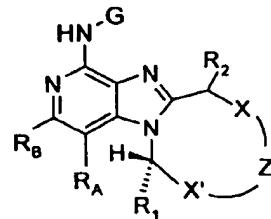
R_4 is bonded to X_1 and R_4 is other than hydrogen; or
 R_5 is bonded to X_1 and R_5 is

5



or a pharmaceutically acceptable salt thereof.

6. A compound of the Formula VI:



10

VI

wherein:

G is selected from the group consisting of:

- C(O)-R',
- α -aminoacyl,
- α -aminoacyl- α -aminoacyl,
- C(O)-O-R',
- C(O)-N(R'')R',
- C(=NY₂)-R',
- CH(OH)-C(O)-OY₂,
- CH(OC₁₋₄ alkyl)Y₀,
- CH₂Y₁, and
- CH(CH₃)Y₁;

R' and R" are independently selected from the group consisting of C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, 5 aryl-C₁₋₄ alkylene, heteroaryl-C₁₋₄ alkylene, halo-C₁₋₄ alkylene, halo-C₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃, -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂, with the proviso that R" can also be hydrogen;

α -aminoacyl is an α -aminoacyl group derived from an α -amino acid selected from the group consisting of racemic, D-, and L-amino acids;

10 Y₂ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and benzyl;

Y₀ is selected from the group consisting of C₁₋₆ alkyl, carboxy-C₁₋₆ alkylene, amino-C₁₋₄ alkylene, mono-N-C₁₋₆ alkylamino-C₁₋₄ alkylene, and di-N,N-C₁₋₆ alkylamino-C₁₋₄ alkylene;

15 Y₁ is selected from the group consisting of mono-N-C₁₋₆ alkylamino, di-N,N-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C₁₋₄ alkylpiperazin-1-yl;

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

20 X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

25 Z is selected from the group consisting of -O- and -N(-Y-R_{2a})-;

R₁ is selected from the group consisting of:

-X₁-R₄,

-X₁-Y'-R₄,

-X₁-Y'-X"-Y'-R₄, and

30 -X₁-R₅;

R₂ is selected from the group consisting of hydroxy, alkoxy, alkyl, and alkenyl wherein the alkyl group can be unsubstituted or substituted by one more substituents

independently selected from the group consisting of alkoxy, amino, hydroxy, and methanesulfonylamino;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

5 halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

10 -N(R₉)₂;

or when taken together, R_A and R_B form a fused aryl or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group;

15 or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

20 hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

25 alkylthio, and

-N(R₉)₂;

R₃ is selected from the group consisting of:

-Z'-R₄,

-Z'-X"-R₄,

30 -Z'-X"-Y'-R₄,

-Z'-X"-Y'-X"-Y'-R₄, and

-Z'-X"-R₅;

X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

5 X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

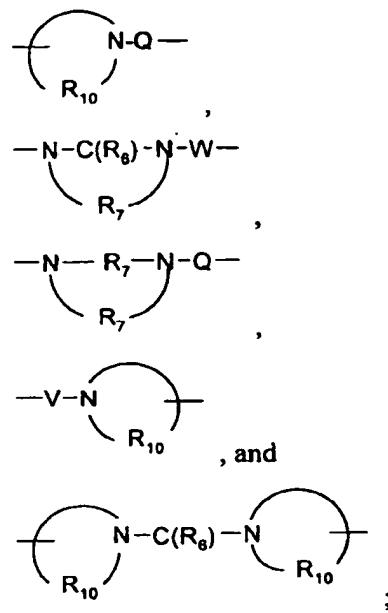
a bond,

10 -S(O)₂-,
 -S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-N(R₈)-,
 -C(R₆)-N(R₈)-C(R₆)-,
 15 -C(R₆)-N(R₈)-S(O)₂-, and
 -C(R₆)-O-;

Y' is selected from the group consisting of:

20 -O-,
 -S(O)₀₋₂-,
 -S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-O-,
 -O-C(R₆)-,
 -O-C(O)-O-,
 25 -N(R₈)-Q-,
 -C(R₆)-N(R₈)-,
 -O-C(R₆)-N(R₈)-,
 -C(R₆)-N(OR₉)-,
 -O-N(R₈)-Q-,
 30 -O-N=C(R₄)-,
 -C(=N-O-R₈)-,
 -CH(-N(-O-R₈)-Q-R₄)-,

5



Z' is a bond or -O-;

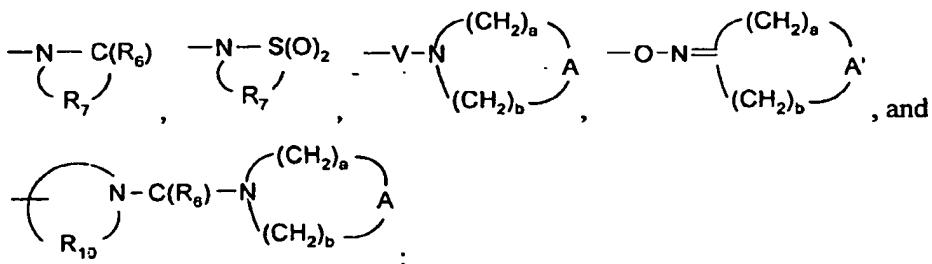
R_{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxy carbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected

from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,

5 oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

10 R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylene, C_{1-10} alkoxy- C_{1-10} alkylene, aryl- C_{1-10} alkylene, and heteroaryl- C_{1-10} alkylene;

R_9 is selected from the group consisting of hydrogen and alkyl;

15 R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, $-O-$, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(-Q-R_4)-$;

A' is selected from the group consisting of $-O-$, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

20 Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

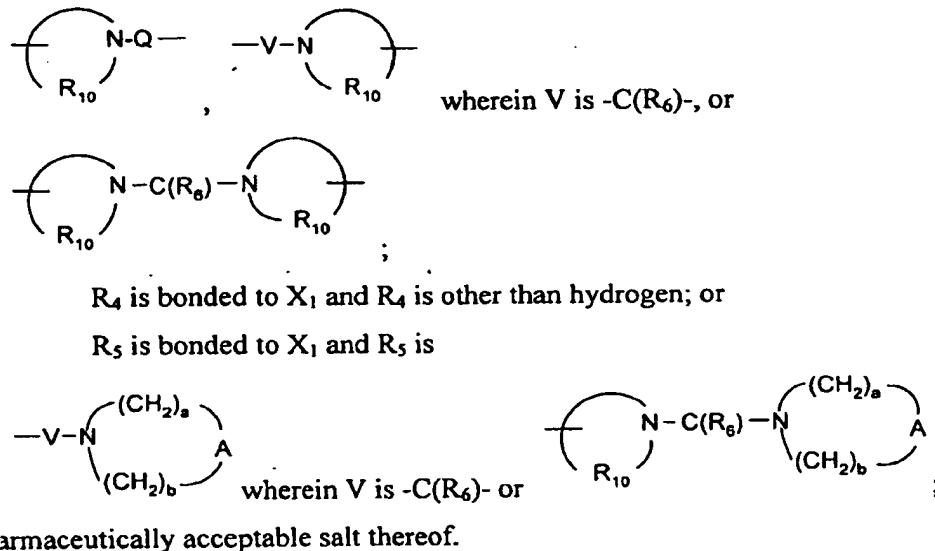
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_{0-2}-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ;

25 with the proviso that X_1 can also be a bond when:

Y' is bonded to X_1 and Y' is $-C(R_6)-$, $-C(R_6)-O-$, $-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,



7. The compound or salt of claim 5 wherein R_{A1} is hydrogen or alkyl, and R_{B1} is alkyl.

10 8. The compound or salt of claim 7 wherein R_{A1} and R_{B1} are each methyl.

9. The compound or salt of claim 3 wherein n is 0.

15 10. The compound or salt of claim 4 wherein p is 0.

11. The compound or salt of any one of claims 3, 4, 9, and 10 wherein m is 0.

12. The compound or salt of any one of claims 1 through 11 wherein Z is

20 -N(-Y-R_{2a})-.

13. The compound or salt of any one of claims 1 through 12 wherein Y is selected from the group consisting of -C(O)-, -S(O)₂-, and -C(O)-NH-.

25 14. The compound or salt of claim 13 wherein Y is -S(O)₂- and R_{2a} is methyl.

15. The compound or salt of any one of claims 1 through 11 wherein Z is -O-.
16. The compound or salt of any one of claims 1 through 15 wherein X is a bond.
- 5 17. The compound or salt of any one of claims 1 through 16 wherein X' contributes one ring carbon atom.
18. The compound or salt of any one of claims 1 through 17 wherein X' is C₁₋₂ alkylene.
- 10 19. The compound or salt of claim 18 wherein X' is methylene.
20. The compound or salt of any one of claims 1 through 16 wherein X' contributes two ring carbon atoms.
- 15 21. The compound or salt of any one of claims 1 through 20 wherein R₁ is -X₁-R₄.
22. The compound or salt of claim 21 wherein R₁ is C₁₋₄ alkyl optionally substituted by hydroxy or one or more fluorine atoms.
- 20 23. The compound or salt of any one of claims 1 through 20 wherein R₁ is -X₁-Y'-R₄.
24. The compound or salt of claim 23 wherein X₁ is C₂₋₅ alkylene, Y' is -NH-C(O)-, -S(O)₂-, or -NH-C(O)-NH-, and R₄ is C₁₋₃ alkyl.
- 25 25. The compound or salt of any one of claims 1 through 20 wherein R₁ is tetrahydro-2H-pyran-4-ylmethyl.
26. The compound or salt of any one of claims 1 through 25 wherein R₂ is C₁₋₄ alkyl optionally substituted by C₁₋₃ alkoxy, amino, hydroxy, and methanesulfonylamino.

27. The compound or salt of claim 26 wherein R₂ is selected from the group consisting of methyl, ethyl, *n*-propyl, aminomethyl, hydroxymethyl, methanesulfonylaminomethyl, and methoxymethyl.

5 28. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 27 and a pharmaceutically acceptable carrier.

10 29. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 27 or the pharmaceutical composition of claim 28 to the animal.

15 30. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 27 or the pharmaceutical composition of claim 28 to the animal.

31. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 27 or the pharmaceutical composition of claim 28 to the animal.

20